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VOLUME VI

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CHAPTER CXXXVI

BODY TEMPERATURE AND ITS REGULATION

By Fritz B. Talbot, M.D.

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Body Temperature.—"Lavoisier was the first to recognize that animal heat was derived from the oxidation of the body substance and to compare animal heat to that produced by a candle."[1] He concluded that the source of heat lay in the oxidation of the body. The law of conservation of energy is generally applicable to all life and we look to the sun and the moon for its source. Heat is the final expression of energy in the human being. The first subject which comes up for consideration is, therefore, what is the normal temperature of infancy and childhood?

Method of Determining Body Temperature.—The earlier investigators and clinicians measured the body temperature by placing the thermometer in the groin or axilla, but recent investigators have shown that the rectal method is the most accurate. In Gundobin's clinic the rectal method is strictly forbidden because he considers that the danger of breaking the thermometer is great. The experience of modern American hospitals shows that such danger is more imaginary than real. In the writer's experience the only danger with this method was that the greased thermometer might slip too far in but it is always easily recovered. The accuracy of the rectal temperature depends upon the distance the thermometer is inserted inside the rectum. It should be introduced 5 cm., because any less than this will not give a true reading in a debilitated child, especially one with cold extremities. The difference in the temperatures taken at 5 cm. and at 2 cm. is greater when the body temperature is low than when there is fever. "The age of the patient, sex, bodily nutrition, relaxation of the sphincter, and presence of feces in the rectum all influence the accuracy of temperatures taken by rectum. When taken with an accurate, though not self-registering, chemical thermometer, the rectal temperature obtained at 7 to 14 cm. was found to be 0.2 to 1.3°C. (0.36 to 2.34°F.) higher than a reading made at 2 to 6 cm. This is not only true of patients with fever but also those without fever and in normal health. These facts were determined in children of different ages, and it was found that the same variations occurred in the six day old child as in the seven months old, eighteen months old child."[2] The axillary or groin temperature is, of course, lower than the rectal temperature.

Temperature of the Fetus.—It has been shown in animals that the temperature of the pregnant uterus is about 1°C. (1.8°F.) warmer than that of the non-pregnant uterus. It may be assumed, therefore, that the fetus takes a part in making its own heat and excretes it through the surrounding tissues as well as through the maternal blood. This assumption is confirmed by the work of Murlin[3] who, by measuring the metabolism of pregnant dogs, while carrying their puppies and after delivery, showed that extra heat, which must have been due to the katabolism of the puppies, was excreted during pregnancy.

Temperature of the Newborn.—The temperature of the newborn infant immediately after birth, before the cooling action of the external air takes effect, is 0.1 to 0.5°C. (0.18 to 0.9°F.) higher than that of the mother. This is due to the extra heat formed by the uterus during the contractions of labor.

It may be assumed that the heat regulating center in the brain does not functionate perfectly during the first days of life and that the body temperature of the newborn, especially if premature, is greatly influenced by slight causes, especially the surrounding temperature. It has been shown that the weaker the child the quicker the body temperature reacts to the surroundings. The following table[4] shows the rectal temperatures of an infant taken at frequent intervals during the early hours after birth.

Time	Rectal temperature		Time	Rectal temperature	
	Degrees Centigrade	Degrees Fahrenheit		Degrees Centigrade	Degrees Fahrenheit
May 14, 1915					
Born 4:01 p.m.					
4:06 p.m.	37.0	98.6	6:44 p.m.	36.0	96.8
4:17 p.m.	37.0	98.6	7:09 p.m.	36.0	96.8
Bath 4:20 to 4:45 p.m.*					
4:46 p.m.	36.4	97.6	7:34 p.m.	36.3	97.4
4:56 p.m.	35.2	95.4	7:59 p.m.	36.3	97.4
5:23 p.m.	35.2	95.4	8:25 p.m.	36.4	97.6
5:49 p.m.	35.4	95.8	8:50 p.m.	36.4	97.6
6:17 p.m.	35.7	96.2			

* Bath (first oiled and then bathed in water, the temperature of which was 102°F. The temperature of the room was 71°F.).

The baby's temperature was normal until the bath, during which so much heat was lost that the body temperature was subnormal for several hours afterwards, since the baby did not manufacture enough heat in its own body to make up for the heat it lost during the bath. The less protected and the more exposed the baby is the lower its temperature falls. Muscular exercise results in the formation of heat so that this baby could have replaced the heat it lost if it had cried or shivered. The crying of a lusty newborn infant, therefore, has the function of supplying heat to its body to replace that lost from exposure incidental to birth, besides the function of expanding the lungs. Subnormal temperatures are more common in the delicate or the prematurely born infants than in the healthy newborn.

The average rectal temperature of infants during the first eight days after birth is as follows:[5]

Age	Number of subjects	Average temperature		Age	Number of subjects	Average temperature	
		Degrees Centigrade	Degrees Fahrenheit			Degrees Centigrade	Degrees Fahrenheit
1 to 12 hours.....	48	36.7	98.1	4 days......	51	37.0	98.6
12 to 24 hours....	26	36.9	98.4	5 days......	41	36.9	98.5
1 day...........	74	36.8	98.2	6 days......	22	37.0	98.6
2 days...........	65	37.1	98.8	7 days......	16	36.9	98.5
3 days...........	62	37.2	99.0	8 days......	9	37.1	98.8

These observations support the views of earlier investigators. It is evident that there is a sudden initial decline of temperature which reaches its minimum usually on the first day. This decline may be attributed to the exposure incidental to birth and during the cleansing bath. The decline in the cases studied by the writer was greater in the weak infants than in the vigorous ones who shivered and cried lustily, and replaced the heat lost by cooling of the body surface with heat which resulted from muscular exercise.

On the second day the temperature reaches the normal but it is usually 8 to 10 days before the heat-regulating function is the same as in older children. The temperature varies with different individuals, and the amount of variation during a given day varies in different babies. After the first week of life there is very little variation in the temperature. The temperature of infants is always higher than adults even with similar diseases.

Influences Which Change Body Temperature.—Many factors seem to play a part in the change of body temperature during the 24 hours; rest and exercise, hunger and digestion, waking hours and sleep may be contrasted and cause greater changes in the temperature of an infant than in an adult.

Many investigators[6] have emphasized in their studies of the metabolism of infancy and childhood the difference between the heat production during absolute rest and exercise. During exercise more heat is formed in the body than during rest. This heat is in a large part radiated from the skin. If the skin does not react quickly to the accumulated heat there is an increase in body temperature. If, on the other hand, the skin perspires there will be a greater radiation of heat due to the evaporation of water. A very good example of this has been given by Lusk[7] in his studies on chills in the malarial adult. During a chill, there may be very little heat lost from the skin, in fact the skin may even be cold, but heat accumulates in the body, thus giving rise to the characteristic temperature. After the patient begins to perspire freely the surface of the skin becomes cool and the temperature commences to fall. It has been found that in infancy hard crying will increase the temperature 0.1°C. (0.18°F.). An even greater increase has also been observed in the temperatures of older children. Funkenstein[8] took the temperatures of 13 children from 4 to 12 years of age who were supposed to be perfectly normal. Six of these children were given physical exercise consisting in arm, trunk and shoulder movements and knee bending. It was found that the temperature of one child increased, while another showed an increase of pulse rate, without an increase in temperature. Other children showed an increase in temperature after 30 minutes' exercise. His experiments showed that after moderate exercise the temperature could materially increase, but that after a short rest it again fell to normal. Wolff[9] found an increase in temperature after exercise in healthy as well as tuberculous children.

During sleep the body temperature can fall markedly as is shown in the following table by Allix:[10]

Age	Normal *A*			Abnormal cases *B*			Greatest and smallest difference in		Average of all cases		
	Awake °C.	Asleep °C.	Number cases	Awake °C.	Asleep °C.	Number cases	*A*, °C.	*B*. °C.	Awake °C.	Asleep °C.	Difference, °C.
0 to 12 days....	37.80	37.20	12	37.7	38.0	4	1.0 0.3	0.5 0.1	37.78	37.40	0.3
5 to 16 months.	37.86	37.07	7	37.6	38.0	1	1.0 0.5	...	37.75	37.14	0.5
20 months to 4 years.	37.70	37.12	8	37.2	37.8	2	1.0 0.0	0.8 0.4	37.60	37.26	0.3

During the first week of life Bärensprung found the average evening temperature somewhat higher than the morning temperature, there being a difference of 0.2°C. (0.36°F.); Finlayson found that the temperature rose slightly during the course of the morning and the early afternoon and fell from 6 p. m. onward reaching the minimum at 3 a. m.

Relation between Starvation and Digestion and Temperature.—There is a very close connection between the rise of temperature and starvation, known as "inanition fever" (Holt and Crandall). This is usually seen during the second and fourth day of life in cases in which the infant gets very little or nothing to eat. These temperatures fall when enough food is given either from the breast or the bottle or enough water is administered. The latter fact suggests the term "thirst fever" (Eric Muller), or "desiccation fever" (von Reuss).

In the light of more recent knowledge it seems established that this fever is due to lack of liquid more than lack of food *per se*. Such infants have a hot, dry skin with prostration and a high temperature. They present a picture somewhat similar to heat stroke in the adult. They are quickly relieved by replacing the deficient fluid in the body.

Aseptic Fever.—A certain number of children who have undergone considerable traumatism during birth have an elevation of temperature for which no explanation can be found. De Uilliers suggested that it might be due to obstetrical traumatism. The fever usually does not last more than two days and it rarely exceeds 39°C. (102°F.). Fever following fractures, hematomas, and tissue contusions in children has also been attributed to the absorption of body proteins.

Starvation in Older Infants.—When an infant is deprived of food a subnormal temperature results and the body functions are carried on at a lower level as was shown in the studies of the metabolism of the newborn by Benedict and the writer.[11] The number of calories of the basal metabolism of babies with subnormal temperatures tended to be lower than those with normal temperatures or even the same infant at another date. There is also the same tendency in atrophic or marasmic infants. When an easily digested and absorbed food is given in these instances there is an inclination for the temperature to return to normal. Sugars, when tolerated, are especially indicated because of their rapid transformation into heat.

Influence of Digestion on Temperature.—Body temperature may also be influenced by digestion, because during the process of digestion extra heat is formed in the body. The part played by the food elements differs somewhat in that the digestion of carbohydrate results in a 5 per cent. increase in the metabolism, fat a 10 per cent. increase, and protein a 30 per cent. increase. It is obvious, however, that the rise in the temperature due to digestion depends upon the quality as well as the quantity of food given. The greatest rise in temperature comes after a meal composed entirely of protein.

Salt Fever.—The administration of 100 c.c. of a 3 per cent. solution of sodium chloride subcutaneously was said by Finkelstein and many of his followers to cause fever. The reaction to be expected is that from four to six hours after the injection the temperature begins to rise rapidly, soon reaching a maximum and then falls slowly so that at the end of 12 hours the temperature reaches normal. It was found, however, that the fever did not result when sterilized salt solutions made with water free from bacteria and bacterial toxins was used. Salt fever, therefore, was found not to be due to salt but to impure water used in the solution.

Recent unpublished observations, however, have shown that salt fever may result from the ingestion of sodium chloride. The skin of the subject turns red and heat accumulates in the body resulting in fever which may reach 104. This presumably is not an increased heat production but a diminished heat loss. The temperature rapidly falls when the skin commences to perspire.

Resistance against Cold.—A young animal is provided by nature with a covering which soon protects it from the cold; the extra heat needed during the first few weeks of life being supplied by close contact with its mother. An infant, however, comes into the world with no such covering and is, therefore, entirely dependent upon artificial heat and warm garments to keep alive and to prevent the body heat from radiating. Its resistance to cold, which is very slight, has been borne out by the fact that in particularly cold winters we have a much higher mortality than in mild winters. As the infant grows older its resistance becomes greater. This is due in part to the fact that with increasing age the relative amount of body surface, from which heat may be lost, diminishes as compared to the body-weight, and also to the great increase of muscular tissue, which "active protoplasmic mass" greatly increases the heat formation within the body. In newborn infants the body temperature may be lowered by exposure to the bath. In older children it may be lowered by exposure, by staying in swimming too long, or by insufficient clothing due to styles. One of the worst habits that parents have is to dress their children in socks during the winter, thus chilling them.

Production of Heat in the Body.—Throughout the whole of the 24 hours heat is being formed in the body to replace that which is lost by conduction and radiation. The source of this heat is the food. The process of converting food into heat depends upon a very delicate and complicated mechanism which is outside the scope of this paper, but which in brief is as follows: The food enters the gastro-intestinal canal where it is prepared by the digestive juices for absorption. The fats enter the blood stream through the lymphatics in their simplest form ready to be either deposited or oxidized. The carbohydrates are all converted into mono-saccharides, absorbed directly into the blood stream ready either for oxidation or to take part in the formation of more tissue. The proteins are broken down into amino-acids, absorbed and used to repair broken down tissues or to build up new tissues. When any of these foods are oxidized heat is liberated and the end result of oxidation, carbon dioxide and water, are excreted from the body.

There is a continuous formation of heat in the body when a child has an empty stomach and is absolutely quiet; this heat when measured is called the "basal metabolism," and is approximately constant in children of the same sex, age, weight and height. It can be predicted within close limits on curves.[13] The formation of heat is dependent upon other factors than the basal metabolism. The digestion of food causes an extra heat formation, the various food element contributing different amounts. More heat is given off by protein than by either fat or carbohydrate, and the fat somewhat more than carbohydrate. Hence, after a large dinner of meat an individual will feel uncomfortably warm on a hot day while no such feeling is experienced after a meal consisting principally of starches. Heat formation also results from muscular exercise in proportion to the degree of activity. The heat production of a newborn infant studied by the writer showed an increase of 200 per cent. over the basal metabolism during active crying for a short time, but this is by no means the rule. In two other instances the amount of heat due to muscular exercise in a normal baby was measured during 24 hours and found to be approximately 25 per cent. of the basal metabolism.[14]

Regulation of Heat Loss.—The greatest loss of heat from the body is by conduction and radiation. The amount of heat lost in this manner depends on the surrounding temperature. When the body is surrounded by a lower temperature than 98.6°F. (37°C.) there will be radiation and conduction, but little evaporation of water from the lungs and skin. On the other hand, when the temperature surrounding the body is the same or higher than that of the body there is no loss of heat by radiation and conduction but a great loss by water evaporation. Although this loss of heat by evaporation has been studied in the adult with modern methods, very little accurate data is available for infants. In adults the greatest loss is from the extremities. The same principle has been shown to hold true in infancy.[15]

It has been shown by Abt and others that there is a difference between the superficial and deep temperatures of the body and the rectal temperatures taken with the thermometer inserted 7 to 14 cm. and 2 to 6 cm. The readings taken with the thermometer inserted 7 to 14 cm. were found to be 0.2 to 1.3°C. (0.36 to 2.34°F.) higher than the readings made at 2 to 6 cm. The gastric temperature has been found to be from 0.09 to 0.2°C. (0.16 to 0.36°F.) higher than the rectal temperature. It is evident from these observations and from animal experiments that blood coming from the internal organs must loose heat to the cooler surface of the organism.

There is also a nervous regulation of heat production and loss. The temperature of the body is kept at a remarkably constant level but when the environment becomes colder than the body, the nerves react and cause a constriction of the peripheral blood-vessels. When, on the other hand, the surrounding temperature is greater than that of the body, the blood-vessels dilate and perspiration and evaporation of water results.

There is an increase of the metabolism as a result of the production of heat in cold surroundings. When the production of heat is not sufficient to keep the body warm, a child shivers. This form of muscular exercise increases the heat production and warms up the body. The physical development of the body also modifies the loss of heat. Fat which is inert so far as the metabolism is concerned acts as a blanket to retain heat. For instance, one may observe with what ease a stout person bathes in cold ocean water while a thin person shivers and becomes blue with the cold. A stout person, on the other hand, suffers during the hot weather, especially if the humidity is high, while a thin person is very comfortable.

Influence of Heat on the Temperature of the Infant.—The heat regulating apparatus in the newborn infant does not take up its functions immediately after birth because it is either undeveloped or incomplete. This is especially true of premature infants who are under the additional disadvantage of lacking the covering of subcutaneous fat which keeps the full-term baby warm. In later infancy, malnutrition causes a great loss of body fat. These infants loose the power they once possessed of maintaining their body heat, and are kept warm with as much difficulty as is the premature infant. The temperature of feeble newborn infants, who are not able to maintain their body heat, may drop as low as 30°C. (86°F.) and still the baby may survive. A subnormal temperature, however, may be brought up to normal by means of hot-water bottles. Lederer[16] showed that a subnormal temperature could be raised to normal by external heat in his investigations in which he used a hollow tin pillow which could be filled with warm water every five or six hours. Woolen blankets were laid on this and the child wrapped up in them. He then had an infant with no demonstrable disease placed upon this warm pillow, and the temperature which was 34.8°C. (94.6°F.) rose to 38°C. (100.4°F.). The baby became restless and cried and the temperature continued to rise to 40.8°C. (105.4°F.). After removing the pillow the temperature fell to 36.7°C. (98.1°F.) in the morning and 35.2°C. (95.4°F.) in the evening. This example shows that when the heat regulating apparatus is not functioning the body temperature can be raised above normal. When infants are submitted to excessive heat their body temperature becomes elevated, they become restless and perspire profusely, and very often the respirations are as high as 186 to the minute. These findings suggest that the metabolism of infants, like that of cold-blooded animals, may be increased, but as yet there have been no experiments to bear out this assumption. The effect of high temperatures, however, is not uniform in all babies because perspiration and proper clothing makes it possible for some of them to loose some of the excessive body heat. It has been found that this is more readily done when a child is without clothes than when it is fully dressed. It is obvious, therefore, that children should be lightly clothed in the summer time. The clothes should be of such a nature that they absorb moisture of sweat and still allow the cooling effect of evaporation.

Practical Considerations of Temperature in Infancy and Childhood.—The heat regulating apparatus of the newborn infant is not fully developed at birth and nature has not supplied him with a means of keeping warm if left to himself. He must, therefore, be protected from exposure as soon as he is born. His birth should take place in a thoroughly warm room and he should be wrapped up in warm clothes as rapidly as possible to prevent undue loss of heat from the body. These procedures are undertaken as a matter of course by all good obstetricians, but unfortunately there still remain some individuals who consider their responsibility ended after they have brought the baby into the world.

It seems probable that the first step towards death has been taken by many babies in their first bath. The water cleansing bath should be dispensed with in the newborn infant. The table on page 2 shows the effect of the water bath on the body temperature. In place of the bath the infant may be easily cleaned with olive oil heated to 40°C. (105°F.), precautions being taken at the same time to prevent exposure. Cleansing with olive oil has the advantage of cleaning the skin satisfactorily and not lowering the body temperature.

These facts which are true of the newborn infant are doubly true of the premature infant. In some cases it is better not to oil the premature infant at all for the first day or two but merely to wrap it up quickly in a warm jacket and keep it warm with hot-water bottles or other well-known methods. It has been shown,[17] that during the period between the baby's birth and the establishment of the mother's milk, the baby subsists on its own body tissues. It uses up first its blood sugar and glycogen; but since this supply is limited, it commences to use up its own body fat after 12 or more hours. This body fat is the fuel which keeps the baby warm until the breast milk "comes in" and supplies an outside source of food heat. It is for this reason that the last month of intra-uterine life is consumed in laying fat onto the baby that is about to be born. The premature infant, however, lacks this advantage and enters the world with a deficiency in subcutaneous fat proportionate to its prematurity. Since there is little or no fat to burn up to maintain body heat it is essential that the body should be fed at once. If it is not fed, the alternative source of heat, the body protein, will be drawn upon. When the body protein is being consumed the situation is serious. The best food for premature infants is human milk, and, if possible, the milk of another woman should be used until the baby's own mother can supply enough for its needs.

Infants with malnutrition are apt to have a subnormal temperature. This depresses all the body functions and is shown by a lowered metabolism. Since it is impossible for a baby to gain with a subnormal temperature, the same precautions and means of keeping the temperature of premature infants normal should be used with these infants. The change from a subnormal to a normal temperature is sometimes all that is necessary to make such an infant gain in weight and strength.

In older children chilling, though a less important factor than in infancy, is responsible for their failure to grow and also for many indefinite ailments. A child should be clothed according to the weather and not the season of the year. Very warm houses and overdressing in the winter are conducive of as much illness as too little clothing. A child who is dressed for the cold out of door climate begins to perspire when it comes into a house heated to 21.1 to 22.2°C. (70 to 72°F.) because of its heavy clothing, and when it again goes out it becomes chilled. It is better always to keep the temperature of the house at 18.9 to 20°C. (66 to 68°F.). Underclothing the child is equally to be condemned. The abominable fashion of making small, delicate children parade the streets in short socks and bare legs should be prohibited in cold weather. If the parents were made to walk the streets in similar attire they would soon be cured of such notions.

The heat formed during the digestion of food also plays a practical rôle in childhood. During the hot summer days, and especially the "dog days," it is better to reduce the amount of meat in the diet and at times to omit it entirely because of the increase it causes in the metabolism out of proportion to the other food components. A carbohydrate diet will keep the body cooler than one containing much fat or protein. During the cold weather, more protein can be taken to advantage for the reasons just mentioned.

When great stress is put on the metabolism as in fever, the circulating supply of sugar is very rapidly burnt up. Since carbohydrates, especially sugars, are usually easily absorbed, they should form a large part of the diet in fever so long as they are digested. They will then replace the sugar which is being so quickly consumed, and also prevent the fat and protein from being consumed. In starvation solutions of 5 per cent. glucose may be introduced directly into the blood so that it will be available for immediate use.

Heat stroke in all probability is connected with desiccation of the body. During very hot weather, a child should be given every opportunity to assuage its thirst, and if nature does not cause him to ask for water, he should be made to drink extra water to replace that lost in the sweat. The same principle holds true especially in the diarrheal diseases when there is an excessive loss of water in the stools. This also results in desiccation of the body and will intensify all the symptoms. A knowledge of the fluid needs of infancy and childhood is to my mind one of the fundamental facts that all pediatrists should know. During starvation of food, very few symptoms appear, if sufficient water is given to the individual.

Elevated Temperatures.—An elevated temperature is one which is over 36.1°C. (99°F.) and although in the strict sense of the word it must be considered to be fever, it is not necessarily pathologic. Certain children seem to have a higher normal temperature than the average run of children. The child who continually has a temperature of from 36.1 to 36.9°C. (99 to 100.5°F.) should of course be thoroughly studied for any nidus of infection in the teeth, glands, tonsils, heart, lungs or kidneys. When these sources of infection are studied and found to be normal, it is usually better to break the thermometer and treat the child like other normal children, since the chances are that he runs a habitually higher normal temperature than does the average child.[18]

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CHAPTER CXXXVII

TYPHOID FEVER

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Definition.—Typhoid fever is an acute disease produced by infection with a special organism, bacillus typhosus.

Historical.—In 1643, Thomas Mills described what was probably typhoid fever occurring in epidemic form among the Parliamentary troops in England. Early in the eighteenth century, Strother referred to a slow nervous fever associated with ulceration of the intestine and enlargement of the spleen. The disease produced a cloudiness or aberration of the mind which has given it its name Typhos, from the Greek meaning cloud. Shortly afterward, Haxham distinguished cases of "putrid malignant fever," or typhus fever from the "slow nervous fever." The differentiation between these two conditions, however, was not clearly made for nearly a century thereafter; although valuable contributions were made to the pathology of typhoid, by Rieddel in 1748, Bailie, 1761, Roderer and Wagler, 1762. Brettonneau, in 1826, called the condition Dothienenteritis, or abscess of the small intestine, and in 1829, Louis in his great work gave the name "Fievre Typhoide" to the malady.

It seems at this time that typhus fever was exceedingly rare in Europe. The two diseases, however, co-existed both in England and in this country; and to William Gerhard, of Philadelphia, a pupil of Louis, is due the credit of having given, in 1839, a convincing basis for the separation of typhus from typhoid fever. He showed that typhus fever was much more contagious and did not produce the lesions known to be characteristic of typhoid. It was felt after this that typhoid was rarely carried from patient to patient; but Budd in 1856 spoke of the danger of transmission in typhoid and affirmed that the poison of the disease lay in the patient's excreta. Murchison traced an epidemic of typhoid to a milk supply contaminated by the stools of typhoid patients.

After the introduction of bacteriology, typhoid fever was one of the first of the human infectious diseases to be studied. Eberth, in 1880, was the first to find the organism in the tissue of a patient; and four years later, it was grown in pure culture outside of the body by Gaffky. Shortly afterwards the typhoid bacillus was demonstrated in the stools, urine, and circulating blood (the latter by Fraenkel and Simonds) of patients suffering from the disease. In 1900, Metchnikoff and Besredka succeeded in producing the disease experimentally in anthropoid apes.

Age and Incidence.—Although typhoid fever has been described from fetal life to extreme old age, it is essentially a disease of youth and early adult life. It is probable, however, as the symptoms are more or less atypical in childhood and in old age, that many cases occurring in these age periods have been overlooked, and that our statistical reports do not give absolutely reliable data. It is certain, however, that typhoid fever is a comparatively rare condition in infancy, and that the number of cases increases through childhood and beyond to about 30 years of age, and that the largest percentage of cases occur in the decade between 20 and 30 years.

In an analysis of 4717 cases among children up to 12 years of age, collected from the literature by Percy, but 2.2 per cent. were under two, 27.8 per cent. between two and five years, and 66 per cent. between 6 and 12 years. Holt asserts that no case of typhoid occurred under two years of age among 10,000 cases of acute illness treated at the New York Infant Asylum, and no cases of the disease have been recognized among the many infants received in the New York Foundling Hospital.

For a number of years, at The Thomas Wilson Sanitarium, which receives each season from between 300 and 400 infants acutely ill with intestinal disorders, the Widal reaction was tried with the blood of every case having fever, and in no case was it positive.

On the other hand, in those communities where typhoid is prevalent among adults, its incidence is not infrequent among young children. Thus Griffith reports 75 cases of typhoid fever in children under 2½ years of age, more than half of which had been under his personal care. Many of these cases were treated some years ago, before the introduction of the sanitary sewerage system in Philadelphia, which has greatly reduced the number of cases in that city. Typhoid fever occurs particularly in the temperate climates in all parts of the world. Osler estimates that in the United States, half a million people have typhoid fever each year, and that 35,000 to 40,000 die. The majority of cases in all ages occur in late summer and fall, although certain epidemics seem independent of the seasons.

It has been notoriously prevalent among soldiers in all recent campaigns, up to the time of the Russian-Japanese War. It has always been more prevalent in permanent camps, where imperfect sewerage and contaminated water supply facilitate the distribution of the bacilli. Modern sanitation has greatly reduced the incidence of typhoid fever in the past European War.

Epidemiology.—In practically all cases of typhoid fever, the infecting organism enters the body through the mouth, usually with food or drink. The typhoid bacillus belongs to a large group of colon-like organisms, and is differentiated from the other members of the group by its cultural reactions. It does not ferment sugar with the formation of gas; it is actively motile and agglutinates usually in high dilutions with the blood of the patients. In the body the typhoid bacilli are not, as was originally thought, confined to the intestinal tract, but enter the circulating blood and are distributed throughout the body. They can usually be demonstrated in the stools in some stage of the disease, but are especially numerous in the duodenum and jejunum. They may persist in certain organs, notably the gall-bladder and the urinary bladder, for weeks, months, and even years after the disease is over. They may even be present in the bodies of persons who have shown no symptoms of typhoid, but have been in close proximity to patients. Outside the body the organism is usually destroyed. In direct sunlight it perishes within a few hours. Under certain favorable conditions, however, it may be viable in the soil or dust for weeks. In milk they proliferate rapidly without producing any change in its appearance or taste.

It is evident, therefore, that typhoid fever is produced by direct or indirect infection of a patient from another patient suffering with the disease. Among adults, contaminated water is the most frequent means of introducing the organism into a susceptible person. This contamination is brought about usually by infection of the water supply through sewage. In infants and young children it is probable that more cases of typhoid are contracted through milk. This may be infected, either by careless handling of the milk by persons who are suffering from typhoid or who have been exposed to it, or by contamination with infected water. A large number of epidemics have been traced to this latter mode of infection. Direct infection of the infant may take place from the soiled fingers of attendants who are taking care of other children suffering from the disease. The necessity of handling the dejecta of infants, particularly of those who harbor typhoid organisms without showing symptoms of the disease, makes this mode of infection relatively easy. Consequently, it is probable that so-called typhoid carriers are responsible for a larger proportion of cases among children than among older people. Flies have been shown to be carriers of typhoid material, and to these pests infants are more exposed than others.

Pathology.—The post-mortem findings in older children are identical with those in adults.

The Intestines.—The lymphoid elements, especially those in the lower end of the ileum, are particularly affected. The Peyer's patches in the small intestine and the solitary follicles in the large colon are swollen and prominent. This condition is due to serous infiltration of these structures, together with proliferation of the endothelial cells. When this exceeds a certain grade, necroses and sloughing takes place, and the formation of an ulcer follows, which usually reaches to the submucosa. The base of the ulcer is smooth and the edges often undermined. In severe cases large areas of the mucous membrane of the ileum may be ulcerated.

In young children the post-mortem findings are less characteristic: ulceration is often absent and the only changes noted in the intestine are moderate infiltration of the lymphoid tissue with swelling up of mesenteric glands. The spleen is enlarged and softened. There is usually a cloudy swelling of most of the organs, particularly of the liver and kidneys.

Hypostatic pneumonia is often found. In severe cases myocarditis can be demonstrated, the heart muscle being soft and of a yellowish-brown color. Thrombosis in the veins, less often in the arteries, is occasionally seen. No constant changes have been demonstrated in the central nervous system. Encephalitis of a mild grade may account for the aphasia sometimes described in children. The frequency in children of secondary infected processes, such as suppuration of the middle ear, purulent joint infections, furunculosis, etc., should be noted. The post-mortem picture of typhoid fever in infants and young children is suggestive of a septicemia.

Fetal Typhoid.—Typhoid fever occurring in pregnant women produces an interruption of the pregnancy in about 65 per cent. of the cases. Apparently it is more common in the early months of pregnancy. It has been abundantly proved that typhoid organisms can pass from the maternal to the fetal circulation through the placenta and be isolated from the blood of the fetus, but this is by no means always the case. It has been held by many that when this transmission to the organs of the fetus does take place, hemorrhagic lesions in the placenta are present. The disease in the fetus is always a septicemia, and the intestinal changes of typhoid fever later in life are absent. A number of cases have been described as typhoid fever in the fetus in which the fetal blood has given a positive Widal reaction. This data of course is unreliable, as the Widal tests may be positive as the result of agglutinins which filter through the placenta to the fetus. The isolation, therefore, of the typhoid bacilli in the fetus is necessary to establish the diagnosis of fetal typhoid.

There is no evidence that the fetus can survive the infection of typhoid bacillus in utero. Death occurs either before or shortly after birth. The examination of the organs of the fetus infected with typhoid bacilli shows usually a slightly enlarged spleen and parenchymatous changes in the organs. There have been many cases in which women have contracted typhoid fever in their pregnancy and given birth to children free from the disease. Specific agglutinins have been demonstrated in the milk of mothers suffering from typhoid fever.

Symptoms.—In Older Children.—In children after five years of age, infection with the typhoid bacillus produces symptoms which are not unlike those occurring among adults. Many of the cases are milder than in older patients. The disease runs a shorter and a more or less atypical course. The period of incubation is difficult to determine accurately. It is probably shorter than it is later in life, averaging from 5 to 14 days. During this period there is an indefinite history of malaise, fretfulness, unwillingness to play, loss of appetite, and usually some tendency to diarrhea. The onset of the disease is more apt to be abrupt in children than in adults. It is ushered in by chill, fever, or headache, and occasionally by a convulsion. During the first week there is usually a continuous increase in the temperature, which may be somewhat more remittent in adults. The pulse is rapid, but the rate is lower than the degree of temperature would suggest. The tension of the pulse is low and often dicrotic; the tongue is furred and dry; the abdomen moderately distended and may be diffusely tender. In children there is, even early in the disease, more tendency to drowsiness and delirium; this condition depends somewhat upon the degree of temperature. The spleen becomes palpable toward the end of the first week, and in a considerable proportion of cases at this time rose spots appear.

The disease usually reaches its height in moderate cases during the second week. The fever remains high. There is increased mental dulness and often diarrhea. Abdominal distension and tenderness increases at this time, and death may ensue from the intensity of the toxemia, which produces pronounced nervous symptoms, or from intestinal hemorrhage or perforation. In cases of less severity, the symptoms usually begin to abate in the second week. The pulse is less rapid and the temperature less continuous. Loss of weight is now especially noticeable.

In the third week the convalescence begins. The temperature frequently reaches normal, the patient becomes brighter, and the appetite returns. In cases of great severity, however, the severe symptoms may persist through the fourth into the fifth week or longer, during which time the child lies in a stuporous delirium. After the third week, moreover, a relapse may take place in children as well as adults. This constitutes essentially a repitition of the disease in a somewhat shortened form, although in some instances the relapse may be more severe than the original infection.

Special Features in Young Children.—Onset.—As a rule, the younger the child the more sudden the onset. The older children often are languid for several days before temperature is noted, whereas in infants, in perhaps a third of the cases, the disease begins abruptly. The most frequent initial symptom is vomiting, less commonly a chill and sometimes, though rarely, a convulsion, followed by a rapid rise in temperature. Occasionally the symptoms simulate meningitis. There may be twitching of the muscles, retraction of the head, and repeated convulsions, although the tendency to convulsions is more frequent at the onset of other acute diseases such as pneumonia and scarlet fever than at the beginning of typhoid. Less often, a rapidly oncoming stupor may persist for several days before other characteristic symptoms appear. Diarrhea is much more common at onset in infancy than later. Cough and abdominal pain and distension are less frequently found; prostration is rarely noticed.

In general, it may be said that typhoid fever attacks an infant more acutely than an adult, and that the (initial) symptoms are chiefly, fever, diarrhea, vomiting and loss of appetite; less frequently, cough, fretfulness, and abdominal pain. As the disease progresses, the following features are to be noticed in young children.

Fever.—The initial rise is more rapid and the duration of the fever has a considerably shorter average than in adults. The temperature is less influenced by bathing. After the first week, even after the initial temperature has been high, the fever curve usually becomes markedly irregular. In a large number of young children, the temperature is more or less irregular and uncharacteristic during the whole course of the illness. The method of fall of temperature also varies greatly in children. It may be rapid or gradual, or at first gradual and then ending in a relatively rapid fall. Often the temperature may become normal in three or five days after the initial drop. In "Griffith's Cases of Typhoid in Infancy," the duration of the fever lasted more than three weeks in 18 per cent., less than three weeks in 81 per cent., and less than two weeks in 35 per cent.; whereas in one infant fever continued for 57 days. In only a small per cent. did the fever rise to 105 or over.

Digestive Symptoms.—The persistence of the appetite for food in young infants is in marked contrast with the usual condition existing in adults during the early stages of the disease. In only a small proportion of cases is the desire for nourishment lessened. It is possible, however, that children continue to take milk regularly because of the thirst created by the fever and not because the appetite is unimpaired.

Vomiting.—Vomiting, although present, does not occur more frequently in typhoid than in the other diseases of childhood. It is not an alarming symptom, although it may occur occasionally throughout the febrile period.

Diarrhea.—The younger the patients, the more tendency there is to an increased number of stools. The diarrhea is not frequent or of severe grade. There is nothing especially characteristic about the appearance of the stool; it is usually thin and fluid and contains an excess of mucus. Blood has rarely been noted. In older children, there is often no diarrhea present. In a few instances in fact constipation has been troublesome. Abdominal distension is frequently present but is rarely of a grade to cause distress or require treatment. The tenderness in the iliac region and gurgling are not often marked. Abdominal pain may vary in degree from mild indefinite discomfort to such intense pain and tenderness as to lead to the diagnosis of appendicitis. It is a prominent feature in about a third of the cases, but does not seem to have definite relationship to the severity of the attack. It is rarely noted in infants.

Respiratory System.—*Epistaxis.*—Nose bleeding, which is frequent in adult cases, occurs rarely in children except at the onset of the disease.

Laryngitis is more often noted in children than in adults. It may be severe and may be followed by ulceration of the mucous membrane or even by more severe involvement of the underlying cartilage with necroses and abscess formation. The symptoms of this complication are aphonia, rasping croup-like cough, dyspnea, and fits of suffocation. *Bronchitis* is very frequently present at the onset of typhoid fever and continues for a variable time, producing cough, but it is not often a dangerous symptom. Pneumonia is referred to as a complication.

Nervous Symptoms.—Nervous symptoms in young children suffering from typhoid are not so marked as they are in later life. There is little evidence of the so-called "typhoid state" frequently found in adults. Usually the nervous symptoms are confined to increased restlessness and irritability, or to signs of increased nervous excitement represented by convulsions, rigidity, and the like. Symptoms referable to the nervous system are, as a rule, dependent upon the height of the fever and disappear when the temperature falls. In a group of cases, however, the meningeal features may dominate the whole picture. This may be due to a real typhoid meningitis, either serous or suppurative, produced by the typhoid bacilli in the spinal fluid, but occasionally similar symptoms occur produced apparently by the toxin of the disease without any demonstrable lesions of meningitis. An example of early and serious involvement of the nervous system in typhoid infection is the following case which came under my own observation:

A child of two years was suddenly seized with a severe general convulsion, followed by high fever. The fever remained continuously high, and there were repeated convulsions during the first week. Vomiting and diarrhea of moderate intensity were also present. The stools were four to six in 24 hours and contained mucus. The abdomen was slightly distended. There was no retraction of the neck or increased reflexes. After 10 days an intensely positive Widal reaction was obtained with the blood of the patient. There was more or less constant delirium, and after several weeks the acute symptoms subsided, leaving the mental processes much impaired. Subsequently both hemispheres of the brain were exposed at repeated operations and a thick plastic pachy-meningitis disclosed. The patient recovered with permanent loss of mentality.

Typhoid psychoses have been described in older children. These may occur with delirium at onset, or during the course of the fever, or in the weakened condition of convalescence. The prognosis is usually good, although for months or even years after the fever distressing neuresthenia with delusions may persist.

The Circulatory System.—The blood in typhoid fever patients shows some changes from the normal, depending somewhat upon the severity of the disease and the incidence of complications. The red cells in children, except in very severe cases, may be but moderately reduced. In 11 children from two to eight years old reported by Chapin, the red cells did not fall below 4,000,000. The hemoglobin is usually reduced in a greater relative proportion than the red cells. The white corpuscles show no increase, nothwithstanding the fever, and in many instances their number is considerably reduced below the normal for the age of the patient. This absence of leukocytosis may be a definite aid in distinguishing typhoid fever from the febrile disorders of inflammatory nature. The leukopenia noted in the typhoid of adults is true also of older children, but apparently is less characteristic in the first years of life. The differential count of the leukocytes usually shows an increase in the large mononuclear cells; and a severe grade of anemia may occasionally follow typhoid fever.

Unless the case is unusually severe there are no marked changes in the strength of the heart beat or in the rate or character of the pulse, except those changes that are common to other febrile disorders. In infants a pulse rate of 130 to 160 with a temperature of 103 to 104 is a common occurrence. Treatment for circulatory failure is rarely necessary in young children. In older children, as in adults, a slow pulse rate is more common than in other acute fevers. There is little change in the blood pressure. From the beginning of the attack there is a gradual fall in both systolic and diastolic pressure during the febrile period, followed by a gradual return to normal in the afebrile period.

In hemorrhage, of course, there is a sharp fall in blood pressure. In nearly all cases in children, especially in those with thin chest walls, a soft systolic murmur is heard during the febrile period over the body of the heart and in the apex.

Cutaneous Symptoms.—The eruption of typhoid fever, the so-called "rose spots," develops earlier in children than in adults. A few scattered spots are usually to be found from the fourth to the seventh day. Apparently they occur somewhat less frequently than in later life; thus in 23,072 cases in children, they were noted in 61 per cent. They are often missed in colored patients. The rose spots consist of flattened reddish macules from 2 to 4 mm. in diameter; they are seen first upon the abdomen, and they vary in number from one or two spots to an abundant eruption over the whole body. They tend to fade and disappear in two or three days often leaving a yellowish discoloration. They usually appear in successive crops in the course of the disease.

Herpes is extremely rare in children as in adults.

Urinary Changes.—There are no alterations in the urine distinctive of typhoid fever, except for the presence of typhoid bacilli in nearly a third of the carefully investigated cases. The urine is usually diminished, with high specific gravity and dark color, and contains a trace of albumin and an occasional hyalin and granular cast. Permanent nephritis is an uncommon sequela. The Diazo reaction is present in the majority of cases, but is only of slight diagnostic value as it occurs in fevers of quite different origin.

The Spleen.—The spleen is enlarged to palpation in about 80 per cent. of all cases. The enlargement is usually noted in the first week and persists throughout the disease, after which it gradually subsides. The spleen may extend 3 or 4 in. below the costal margin. The organ is generally reduced in consistency and may feel almost soft to palpation. In rare instances the engorgement of the spleen has been of such a grade as to produce rupture.

Relapse.—Relapse consists in the return of fever and other symptoms of onset after several days of normal temperature. The average time of the occurence of the relapse is eight days after the fever has subsided; a true relapse, however, may occur after but three or four days, or may be delayed for several weeks. In many instances several relapses may recur in the course of a long illness. Children show rather an increased tendency to relapse. This feature was noted in 10 per cent. of 1000 cases investigated. Griffith reported relapses in 15 infants out of 75, the duration ranging from 5 to 19 days. The relapse is usually less severe than the original attack. It must, however, be sharply distinguished from a return of fever due to the onset of a complication.

Complications.—In a disease such as typhoid, associated with continued fever and debility, complications are frequent. They are more common in older children and in adults, in whom the disease is of longer duration, than in infancy.

Intestinal perforation occurs in about 1 per cent. of all cases of children under 12 years of age. It was not noted in the 75 cases under 2½ years reported by Griffith. It is more frequent in the severe cases, but may occur suddenly, without any premonitory or other alarming symptoms. It is usually accompanied by sharp, often paroxysmal, pain in the hypogastric region, associated with muscle spasm and rigid abdominal walls. At first the temperature usually rises and then falls rapidly; the pulse and respiration are increased in rate. After a few hours, symptoms of general peritonitis may supervene. Perforation is an exceedingly grave complication, unless the diagnosis is promptly made and surgical interference undertaken.

Intestinal Hemorrhage.—This is more frequent than perforation but is limited sharply to older children, in whom the disease simulates that of adults. It is reported in from 3 to 4 per cent. of cases under 12 years of age. It occurred once in Griffith's series. It may complicate perforation or precede it. The symptoms depend upon the amount of blood lost and the previous condition of the patient. There is usually a fall in temperature with symptoms of general collapse. Hemorrhage occurs most frequently when convalescence begins at the time the ulcers of the intestine are sloughing.

Pneumonia.—Bronchitis is so frequently present at the onset of typhoid, that it has been described as a symptom. Pneumonia forms one of the most serious and frequent complications in typhoid at all ages. It was present in 10 per cent. of Griffith's cases. The process is usually found to be due to the pneumococcus. The complication as a rule sets in during or after the height of the fever when the resistance of the patient is lowered. In a few instances typhoid bacillus has been isolated from the consolidated lung tissue.

Pleuresy, with effusion, or empyema, as is so often the case in childhood, may follow pneumonia.

Myocarditis is not infrequent. It was present in 1 per cent. of our cases and is due to a weakening of the heart walls after a long febrile illness.

Pyelonephritis is more frequently present in typhoid in childhood than in later life. It may be due either to the presence of typhoid organism or, as is more frequently the case, to the colon bacillus. Pyuria may be present after the symptoms of the typhoid have subsided. It occurred in 8 per cent. of our cases. It is probably often missed in infants because of the difficulty of procuring urinary specimens.

There is a distinct tendency in typhoid fever, especially among children, to the occurrence of suppurative processes. Thus in Griffith's cases, 25 per cent. suffered from some form of suppurative complication. The more common of these complications are: Otitis media, which was present in 12 per cent. of the Harriet Lane cases; furunculosis, parotitis, and abscesses in various parts of the body. Bed sores are frequent in protracted cases, unless the nursing care is most efficient.

Inflammation of the gall-bladder with occasional formation of gall stones, is much more rare in children than in adults; but it must be remembered that typhoid organisms may be harbored for long periods in the gall-bladder and give rise to no symptoms.

The hair usually falls out after severe typhoid, but baldness is rare. The lesions of the bones occasionally occur after typhoid. They consist in a periostitis or ostitis and are more frequent in the lower extremities than elsewhere. These lesions are chronic and tend to recur.

Summary.—In summary it may be said that the typhoid bacillus not infrequently affects children over five years of age producing symptoms which are, in the main, similar to those of typhoid fever in the adult; the incidence however, of the infection increases with the age. In general, the disease in young children is less severe and of shorter duration, and recovery results in a larger proportion of cases. Numerous complications may occur, many of them suppurative in character. The localization of lesions in the intestinal tract is less constant in children than in adults. In infants the disease is exceedingly uncommon, and follows a much more irregular course, so that its diagnosis through clinical symptoms is difficult. The intestinal lesions are less common, the organisms are more frequently found in circulating blood, and the whole picture is more apt to be that of a general septicemia. In young infants the mortality rate is high, varying, it is claimed, from 10 to 50 per cent.

Diagnosis.—The diagnosis of typhoid fever in infants and young children cannot be made with certainty from clinical symptoms alone. In all cases where there is continuous fever, or where there is otherwise unexplained malaise and listlessness, the possibility of infection with the typhoid organism should be considered. In such cases, the occurrence of rose spots and the enlargement of the spleen render the diagnosis of typhoid fever probable. Fortunately, however, the diagnosis can often be rendered positive by certain laboratory tests. The most definite of these are:

(*a*) Isolation of the typhoid bacillus from the circulating blood of the patient. With improvement in our technique and more suitable culture media, the organism is recovered in an increasing proportion of cases each year. In 43 cases in our series, in which blood culture was made, the organism was isolated in 33 instances, or in about 76 per cent. This procedure is particularly valuable, as the cultures are more apt to be positive in the first week of the disease when diagnosis is particularly desirable.

(*b*) The isolation of typhoid bacilli from the stools of the patient likewise gives positive evidence of the existence of the disease. This procedure is often difficult because specific organisms are not often found until later in the illness. Improved technique and special culture media have also rendered this procedure much simpler. It is probable that cultures from the duodenum, by means of a duodenal catheter may facilitate the isolation of the organisms from the intestinal tract.

(*c*) The isolation of typhoid organisms from the urine is quite possible, and when obtained, even early in the disease, give reliable information. It should be emphasized, however, that the presence of typhoid organisms in small numbers in the body of patients who do not present symptoms of infection, is not sufficient evidence upon which to base the diagnosis of typhoid fever. Typhoid bacilli may frequently be found in the bodies of patients who have had typhoid fever months or even years before. They may also be found, though very rarely, in persons presenting no symptoms of the disease, who have been in immediate contact with patients, or who have handled material infected with typhoid organism.

(d) **The Agglutination Reaction.**—This test, devised by Greenbaum and adapted by Widal for clinical purposes, depends for its action on the power of the blood of typhoid patients to agglutinate the motile typhoid bacilli in fluid culture media. This test can be carried out under the microscope in drop cultures when the individual organisms mixed with the blood serum of the patient, often in high dilution, can be seen to lose their motility and to gather into large masses or clumps. The test can also be performed by mixing the bacilli with large quantities of blood serum, in small test tubes. The precipitation of the organisms in fine granular masses or sediment, leaving a clear fluid above, indicates a positive reaction. This tests shows the presence in the blood of the patient of agglutins specific for the typhoid organism, and affords positive proof that the patient either has typhoid fever at the time of the investigation, or has had the disease previously, or that he has been treated with typhoid vaccine. The Widal reaction rarely occurs during the first week of illness. Often it cannot be obtained for a much longer period. It is, therefore, more serviceable as a confirmatory indication than as a means of early diagnosis. Recent improvement, however, in the technique of performing the agglutination reaction has rendered this procedure serviceable in those cases which have either already had typhoid, or have been vaccinated. If in cases where the dilution of the patients' serum which will agglutinate typhoid organisms is known and constant, it is found, on subsequent examinations, that there is a marked rise or fall in the agglutinating power of the serum, it is clearly evident the disease is again developing actively. A rise in the agglutinating power indicates the beginning, a fall, indicates the later steps of the infection. In general, the height of the Widal reaction is reached at about the twentieth day of illness.

(e) **Typhoidin Reactions.**—Gay and Force have suggested that an extract of typhoid bacillus, prepared in the same manner as Koch's tuberculin, might be used as a skin test to indicate the presence of typhoid antibodies in the body. Up to this time, however, the test has failed in the hands of the investigators, notably Austrian and Bloomfield, to furnish reliable data. The same material in dilution has been instilled into the eye; a typical reaction produces congestion in a few hours. It is too early to speak of the value of this test. Unusual modes of onset, which as has been said, are more common in childhood, often make it difficult to distinguish the symptomatic diagnosis of typhoid from meningitis. The onset, with its meningeal symptoms, suggests cerebrospinal meningitis. In the latter disease, however, the fever is more irregular and the stiffness of the neck usually more pronounced; and the lumbar puncture yields a turbid fluid containing a specific organism. The spleen is not enlarged as in typhoid and there are no rose spots.

Differential Diagnosis.—From Pneumonia.—Pneumonia, as has been said, may be present at onset or occur late in the course of typhoid fever. High continuous temperature and drowsiness when physical signs of pneumonia are absent may lead to uncertainty in differential diagnosis for several days; especially in young children when the respirations are rapid because of the fever. The high leukocytosis, the absence of enlarged spleen and rose spots, suggest pneumonia. Pulmonary involvement can often be detected by *x*-ray examination earlier than by physical signs.

From Malaria.—The diagnosis of malaria should be made by finding the parasite in the blood. The enlargement of the spleen, the low leukocyte count may be similar in both conditions. The positive Widal test or the isolation of the typhoid bacillus is of course conclusive of the existence of this diease, as is also the affect of quinin in malaria.

From Ileocolitis.—The inflammation of the intestinal tract, such as is associated with diarrhea is, as has been seen, common in childhood cases of typhoid fever. When these diarrheal discharges contain an excess of mucus, as they usually do, and occasionally a little blood, a diagnosis of ileocolitis is strongly suggested. The great rarity, of typhoid fever in early childhood, when ileocolitis is most common, should make one hesitate to diagnose typhoid from the above symptoms, unless in addition to these symptoms the bacillus is isolated or the Widal reaction positive. In ileocolitis the onset is usually more abrupt and the constitutional symptoms at first less severe, even after the stools become muco-purulent. There is also in ileocolitis a considerable increase in the leukocytes and rarely enlargement of the spleen. The temperature is as a rule not so high, and intermittent in type.

From Miliary Tuberculosis.—In childhood, this condition may easily be confused with typhoid fever. There may be the same continuous fever, prostration, and occasionally diarrhea, with enlargement of the spleen. The spleen in miliary tuberculosis, however, is firmer, and the enlargement occurs later in the disease. Respirations are usually more rapid. Frequently one or more patches of consolidation can be found in the lungs or enlarged lymphatic glands can be demonstrated. There are no rose spots. The leukocytes, although low in both diseases average higher, in miliary tuberculosis. In young children a positive von Pirquet reaction is an aid in diagnosis although in some cases only the demonstration of typhoid organisms leads to absolute certainty. In all puzzling cases the family history and environment of the patient should be given due weight.

From Pyemia.—The presence of suppuration in the body may cause continuous fever associated with prostration and loss of weight, and so bring about a condition resembling typhoid fever. In these cases, however, there is nearly always a marked leukocytosis. The Widal reaction is helpful and the cultures from the blood may yield the causal organism. There is no limitation to the duration of the infection.

From Appendicitis.—The severe abdominal tenderness and distension that occasionally occur at the onset of typhoid have led to the diagnosis of appendicitis. In this latter condition, however, the leukocytes, the localization of the pain, and the more rapid progress of the disease should enable one to differentiate it from typhoid.

From Paratyphoid Fever.—This disease has been rarely recognized in early childhood. It is impossible merely from the clinical symptoms to differentiate it from typhoid fever. One must rely upon the agglutination reaction or the isolation and identification of the organism. The symptoms of paratyphoid are discussed in the following section.

Prognosis.—The death rate from typhoid fever under 12 years of age varies considerably with the age of the patient. Children between 5 and 12 years usually stand the disease well, and death, when it occurs, is the result of a complication. The mortality rate at this age period averages about 5 per cent. High fever, marked abdominal distension and hemorrhage are unfavorable symptoms. Occasionally, the mortality rate among younger children, particularly in those under two years of age is considerably higher than has been indicated, the average rate in all such cases being about 12 per cent. In many instances, even in young infants, the disease runs a favorable course. Thus in five children, in the Harriet Lane series under two years of age suffering from typhoid fever in every instance where the organism was isolated from circulating blood, recovery followed. Of the 45 cases between 2 and 12 years, there were but two deaths.

Prevention.—Typhoid fever is a community disease and can be practically eliminated where certain simple hygienic measures are carried out. The typhoid bacilli, the recognized cause of the disease, have no natural habitat outside the human body. Each case is infected directly or indirectly from a previous case which harbors the organism. Typhoid fever is rarely, if ever, conveyed through the air, but rather through the ejecta and secretions of patients. Its prevention consists therefore in disinfection or proper disposal of all infected material. Especially should the water supply of a community be guarded. It has been shown, moreover, that persons who have had typhoid fever may still harbor and secrete bacilli for an indefinite period after recovery. All convalescent cases, therefore, should be kept under observation until the urine, feces, and sputum are free from typhoid bacilli. In most communities where these precautions are not generally practiced drinking water should be boiled and the milk scalded or pasteurized, and care should be taken to avoid eating uncooked vegetables, fruit, etc., where there is any chance of their contamination.

The principle reason that the disease is so infrequent in infancy is because as a rule both milk and water furnished the infants are boiled or pasteurized. Nurses of typhoid cases in hospitals or in homes, being frequent carriers of the disease, must be particularly careful to disinfect their hands before coming in contact with other patients.

Anti-typhoid Vaccination.—Vaccination with a suspension in salt solution of killed typhoid bacilli, has been shown to convey a high degree of immunity to typhoid fever. The experience in the armies of European countries and of England, and in our own army where typhoid vaccination was introduced in 1909 under the brilliant leadership of Maj. F. F. Russell, has shown that in this way typhoid fever can be practically eliminated. This method of prevention should be used much more frequently in children than is customary. Hundreds of children have been vaccinated with no harmful effects, and rarely if ever has a properly vaccinated child contracted typhoid fever. The dose should be regulated according to the weight of the child. A child of 60 lb. for instance should receive half the adult dose. The immunity lasts at least three years. Doctor Russell suggests that it is advisable to vaccinate (i.e., a series of two or three inoculations), once in infancy, once in childhood, once in youth, and once in adult life. If this practice were followed, probably complete protection would be given to a child throughout its whole susceptible period. When we consider that children under 12 compose about one-quarter of an average population and furnish about one-quarter of the cases of typhoid fever, the importance of a more general introduction in our civil population of this adequate means of preventing typhoid fever must be apparent.

The average adult dose of vaccin is 500,000,000 killed organisms, followed in one week by 1,000,000,000 and in a second week by another 10,00,000,000 organisms. As will be indicated in the section on paratyphoid fever, it is possible to give vaccin for both diseases at the same time or in alteration.

In recent years Besredka has introduced a method of oral vaccination. This method is especially recommended for immunization. The patient is first given a small quantity of bile in a gelatine capsule and the dead bacilli (vaccine) immediately after in tablet form. Three doses, one each succeeding day, are necessary. Favorable results have been reported by this method in immunizing against typhoid, paratyphoid, A and B, and dysentery. The value of this procedure in the treatment of these diseases has not been so convincing.

Treatment.—The treatment of typhoid fever by specific therapy is still in its experimental stage. Many investigators have reported favorable results with this form of treatment. It is claimed that the duration of the fever has been shortened and the severity of the symptoms lessened. In 1893 Fraenkel began the use of small doses of killed typhoid bacilli injected hypodermically. Since then, this method of treatment has been tried with various modifications by many physicians.

The results, however, have never convinced the profession of their success. Favorable reports in the hands of one investigator have not been confirmed elsewhere. Wright, after his experience in treating typhoid cases among British soldiers with vaccin, is confident that the treatment is specific and helpful. Chantemesse and others have proposed a serum treatment obtained from horses immunized against typhoid toxin. The typhoid toxin, however, is an intra-cellular one and does not lend itself to the production of antitoxin; differing greatly in this respect from diphtheria and tetanus toxins. It is therefore unlikely that treatment with so-called immune serum will prove beneficial.

In the last few years, following long experimental investigation, Gay has suggested the use of sensitized vaccin, that is, bacilli grown in the presence of immune serum and then destroyed by heat. The vaccin, in a case of typhoid fever, is injected directly into the circulation. The adult dose is approximately 0.04 mg. of the vaccin, which corresponds to about 100,000,000 bacteria. A single injection is usually sufficient. This is followed in a short time by rise in the temperature, often with a chill, and a fall in the number of white blood corpuscles.

About 6 to 12 hours after the injection, the temperature falls to normal and there is a corresponding rise in the leukocytes with subsidence of other symptoms, delirium, etc., characteristic of the disease. It has been shown that typhoid organisms leave the circulating blood after this treatment. Gay was able to apply this treatment in considerably over 100 cases. In 40 per cent. the improvement noted was permanent. In 25 per cent. the patients were bettered and the disease apparently shortened. These cases received several injections.

In a third of the cases, mostly of the severe type, no improvement was noticed, but the treatment was without harmful effects. The beneficial results Gay thinks, are due to the increased number of leukocytes and antibodies in the blood. Confirmation of these results will be required before this treatment can be recommended for general use. It ought only to be attempted in hospitals where its effect can be carefully studied. It is presumed that the dosage in children would be reduced in correspondence with their weight, as is the case with immunizing vaccin.

Nursing Care.—A favorable outcome in a case of protracted fever such as typhoid, depends to a considerable extent upon the general care and management of the patient. Certainly the danger to a household, to other hospital patients, and to the community at large can be reduced to a minimum if the nursing of the patients is conscientiously and intelligently carried out. In general, it is thought best to remove cases of typhoid fever, to a well-equipped hospital. Typhoid patients should be partially isolated and the room well ventilated. In moderate weather they should spend most of the time on a protected porch. The beds should be small so that the patients can be lifted easily and the mattress should be soft for fear of bed sores. Facilities must be at hand for the careful disinfection of stools, urine, and sputum, when there is a cough.

All linen used about the patient should be soaked for two hours in 1:20 carbolic, or in 1:2000 bichloride solution, before sent to the laundry. There it should be boiled. The nurse should wear a rubber apron when working over the patient, and this should be washed frequently with the same solutions. It is safe, too, to wear rubber gloves when washing the patient.

In the nursing of infants and young children, scrupulous care must be taken of the soiled napkins. They must be promptly removed and placed in an antiseptic solution. There should be a rubber sheet over the mattress and the bed linen should be frequently changed.

Diet.—Typhoid fever patients are no longer starved and their diet restricted to egg albumen, and milk as was formerly the case. One of the principal features of typhoid fever in the past has been the loss of weight and with this, consequently, a lowered resistance to complications and an increase in nervous symptoms. It has been found that typhoid fever patients have a remarkable capacity to assimilate food, and that when the diet is carefully balanced, a weight equilibrium can often be obtained throughout the illness. The diet should be rich in carbohydrate, which not only provides the patient with readily assimilable food, requiring a minimum amount of digestive energy, but also prevents the rapid destruction of body tissue with the loss of nitrogen, which is characteristic of typhoid fever.

La Fetra has reported a series of 48 cases in children treated at Bellevue Hospital, to whom a liberal diet was given. They ranged in age from 2 to 12 years. The complications were few; the duration of the disease apparently shortened, and the mortality less than 2 per cent. Sixty per cent. had gained weight during the course of the fever. Eggs and toast, cereals, potato, ice cream, junket, gelatine, etc., were used in addition to milk. The children were fed at three hour intervals, between 6 a.m. and 9 p.m., six feedings in 24 hours. It is worth while to give several typical diets in detail.

On the nineth day, temperature 100 to 103, 2430 calories.

6 a.m.	4 oz. milk, 2 oz. cream, ½ slice bread, 1 egg.
9 a.m.	cocoa 4 oz.
12 m.	4 oz. milk, 2 oz. cream, 1 oz. milk-sugar, 1 egg. 1 slice bread.
3 p.m.	4 oz. milk, 2 oz. cream.
6 p.m.	4 oz. milk, 2 oz. cream, 1 oz. milk-sugar, 1 egg, 1 slice of bread.
9 p.m.	4 oz. milk, 2 oz. cream.

Another diet on the fourty-ninth day of the disease containing 2214 calories, is as follows:

6 a.m.	4 oz. milk, 2 oz. cream, 2 eggs, 2 slices of bread.
9 a.m.	5 oz. of milk, 2 oz. of cream, 3 crackers.
12 m.	3 oz. of potatoes, 1 egg, 1 slice of bread, 6 oz. milk, 2 oz. cream and 2 dr. milk-sugar.
3 p.m.	1 oz. ice cream.
6 p.m.	1 oz. apple sauce, 4 oz. milk, 2 oz. cream, 1 slice of bread.
9 p. m.	4 oz. milk, 2 oz. cream, 2 dr. of milk-sugar.

It will be seen, therefore, that considerable variety of readily digested nutritious foods can be given children in typhoid fever with beneficial results. The calorific value of each diet should be roughly tested. This test can be made with the aid of a simple diet list, upon which is placed the number of calories in a given quantity of each of the foods usually used. In a few cases in convalescence, patients are able to utilize foods having a calorific value of nearly 300 calories per kg., without deleterious results.

Of course, each case should be fed according to its own digestive capacity. Where there is distension and undigested food in the stools, the diet should be simplified. In these cases buttermilk or Eiweissmilch is often helpful. Water should be given freely at regular intervals. A child of five years should take 1 qt. a day. Where there is such long continued delirium or coma as to interfere with deglutition, fluid diet should be given by gavage at regular intervals, not oftener than every four hours. Rectal feeding is rarely helpful. We have little evidence that food is assimilated when it is introduced into the bowel, especially when the colon is irritated as in typhoid fever.

Hydrotherapy.—Altogether the most efficient means of combatting the nervous symptoms of typhoid fever or of reducing temperature without injury to the patient, is through the application of water. This method was suggested by Curry in England in 1777; and made use of by a number of practitioners afterward, but it was not brought into general notice until nearly a century later by Brand. The water can be applied by tub bath, by cool sponging, or by a cool pack. Young children do not stand the bath as well as adults. The first bath should always be given in the presence of a physician and this treatment discontinued if untoward symptoms follow. Children bear fever well, and if nervous symptoms are not a prominent feature, a bath is rarely indicated for a temperature under 104. The child should be placed in a tub upon a canvas support, with the head resting upon a rubber pillow. The temperature of the water should be between 95 and 100, and gradually lowered to 90, or 85, seldom lower. The duration of the bath should be from 10 to 15 minutes, and during this time the body should be actively rubbed. The bath has often a marked effect in controlling nervous symptoms. It increases excretions from the kidney, raises the blood pressure, and improves the condition of the skin so that furunculosis is less frequent. Without question the introduction of the tub treatment has considerably reduced the mortality of the disease in adults.

Sponging.—It has been found, however, by careful clinical observers that many young children do not react well after a cool tub bath. In these cases more beneficial results can be obtained by tepid sponging. For this purpose, tepid water to which may be added a little alcohol, may be used. The child is placed on a large bath towel and sponged limb by limb until after 10 or 15 minutes the whole body is covered. The effects after sponging are perhaps less striking than after a tub, but the danger from shock and collapse is much reduced.

Pack.—In certain instances, a cold pack can be substituted for other forms of hydrotherapy. The pack is given by wrapping the child in a sheet wrung out in tepid water and the temperature further reduced by the addition of cooler water or by fanning. The patients may remain in the pack for one-half hour. The form in which hydrotherapy is to be applied must be determined in every case by the physician, and if used at all must be so modified as to meet individual symptoms.

Mention has already been made of the importance of having patients take a large quantity of water by mouth. This is one of the best ways of reducing temperature, and controlling toxic symptoms. In children particularly, irrigation of the colon with saline solution, is also helpful. With rather cool solution, such an irrigation properly given may reduce the temperature fully as effectively as a sponge or a pack. Often the secretion of urine is greatly stimulated. In very exceptional cases in children when there has been loss of fluid with dryness of the tissues, subcutaneous infusions of salt solution have proved distinctly helpful. One hundred to two hundred cubic centimeters can usually be introduced under the skin in a single infusion. When, however, the pain of the infusion produces increased restlessness, so as to fatigue the patient, it should be discontinued.

Medicinal.—The use of drugs in typhoid fever has been largely discontinued. Antipyretics are dangerous, although an occasional dose of phenacetine or antipyrine may be warranted to meet certain nervous symptoms. Intestinal antiseptics in the treatment of typhoid are being used but little by physicians of large experience. For profuse diarrhea, some astringent treatment is indicated. The best form of this treatment is bismuth sub-nitrate, sub-carbonate or subgallate, in doses of 5 to 20 gr. at three hour intervals. To this, if there is no distension, may be added a few drops of paregoric. Starch and opium enema may also be helpful. In diarrhea the food should be carefully selected and given in as concentrated a form as possible.

Constipation may be troublesome with children in typhoid fever but is sufficiently corrected by occasional enema or the use of mild saline, such as milk of magnesia in small doses, administered perhaps every other day. The abdominal distension which occurs less often in children than in adults may be relieved by the passage of the stomach tube, if the excess gas is in the stomach, or by a rectal tube and the application of a turpentine stupe, if the intestines are distended. A diet low in carbohydrates is indicated. Small doses of salol or charcoal, or in extreme cases, hyperdermics of eserine or of petuitrin have proved helpful. When there are signs of failure of circulation, stimulants are indicated; strychnine, digitalis, and caffeine sodium benzoate by mouth or hypodermically are useful. In sudden collapse, hypodermic of camphor dissolved in oil or ether give prompt results.

Intestinal hemorrhage requires absolute rest, often the use of stimulants. A cold compress should be placed upon the abdomen and ice should be given by mouth. Occasionally, a life has been saved by blood transfusion. The indirect sodium citrate method is the most applicable. Calcium lactate in doses from 5 to 10 gr. may be tried.

The persistence of active typhoid organisms in the urine requires treatment. Hexamine has proved to be our most efficient means of curing this typhoid bacilluria but, it is effective only when the reaction of the urine is acid. Occasionally large doses of soda or other alkali, rendering the urine strongly alkaline is more helpful in these cases, as in pyuria from colon bacillus infection. Typhoid vaccin given in comparatively large doses in intervals of 10 days, should be tried in persistent cases. No patient, in whom this bacilluria persists should be discharged from a hospital or allowed to pass from observation.

In Convalescence.—Children convalescent from typhoid fever still require careful oversight as to their diet and daily routine. Solid food such as meat and coarse vegetables should not be given for a week or two after the temperature is normal, and then only in small quantities.

Convalescent patients should be in the open air as much as possible and guarded from all excitement. A return to school should not be permitted until complete physical and mental recuperation has taken place.

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CHAPTER CXXXVIII

PARATYPHOID FEVER

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Definition.—Paratyphoid fever is a febrile disease due to infection with one or more types of bacilli belonging to the so-called enteric group and closely related to the bacillus typhosus, but distinguishable from the latter by cultural differences and by agglutinations reactions.

Historical.—The organism was first described by Archard in France, in 1896. One of his cases was that of an infant seven months old, who had an attack of apparently mild typhoid fever, followed by suppuration of the sternoclavicular joint. The bacillus was cultivated from the pus.

There are probably a considerable number of slightly different organisms belonging to the enteric group, including the bacillus coli, the paratyphoid (A), paratyphoid bacillus (B); and bacillus typhosus. Bacillus enteriditis of Gärtner, and bacillus psittacosus are closely related. Schott Müller divided the paratyphoid organisms into two groups—Alpha and Beta; Alpha resembling more the colon bacillus in cultures, and Beta, the typhoid bacillus. Both organisms give rise to typhoid like symptoms. Cases have been described by a number of observers abroad and in this country, which have been attributed to one variety of organism or the other; occasionally to both together, or in combination with the typhoid bacillus. In recent years the number of cases in the United States have rapidly increased in frequency. Infection with paratyphoid bacillus (B), seems to be more prevalent. Recent reports from medical officers having care of the military forces in the European war would indicate a wide-spread prevalence of paratyphoid fever at most of the fighting fronts. The majority of cases are said to have been contracted from soldiers, who either have come from India where the disease is rife, or have been in contact with those who have come from the East.

The frequent mildness of paratyphoid, is one of its serious aspects in camp, as the ordinary case with its comparatively slight degree of fever and malaise, may not report for observation and in the meantime may carry the disease to others.

Symptoms.—The onset is more frequently gradual than otherwise, the fourth being the average day for the soldier to report sick. Increasing lassitude, chilliness, sense of illness, headache with or without pains elsewhere, are the early symptoms. General abdominal pain which passes away in a few days, is present in about half the cases.

Diarrhea is often present. Epistaxis is rare and cough is less frequent than in typhoid fever.

In other cases the onset is rapid, and the pains in the head and body, the chilliness, the diarrhea, come on quickly so that the patient is soon prostrated. Vomiting may be a feature of this type of invasion, causing the clinical symptoms resemble that of food poisoning or of some form of gastro-intestinal infection.

Fever.—The fever is lower, remits at an earlier stage and has a shorter duration than that of typhoid. Toward the end of the third week the temperature is often normal and the patient correspondingly improved. The pulse rate is characteristically slow in relation to the temperature. A rapid pulse indicates an unusually severe infection. The tongue is heavily furred on the dorsum, while the tip may be smooth and glazed. The abdomen is rarely distended, and the tenderness of the earlier stages of illness does not persist.

The bowels, often loose at the beginning, are usually constipated after the first week. The so-called "pea soup stool" of typhoid fever is rarely seen. Rose spots occur in crops after the first week, and they continue to appear after the temperature has fallen. They are occasionally large and their edges are less marked than in the spots of typhoid fever. The rash in paratyphoid (A), is said to be more profuse than in that of paratyphoid (B). Reinfections are not uncommon. Tachycardia sometimes comes on after the temperature falls, and delays recovery. Other forms of cardiac irregularity are not uncommon.

The spleen is enlarged clinically in about the same proportion of cases as in typhoid fever. In adults, three types of the disease may be recognized:

1. Those which are similar to typhoid in all respects, these comprise about a third of the cases.
2. Those in which there are severe gastro-intestinal symptoms; about 10 per cent. of the cases.
3. Those of low fever and short duration, nearly 60 per cent. of all cases.

In Young Children.—In a majority of the established cases of paratyphoid fever in young children, the gastro-intestinal symptoms, vomiting and diarrhea, are prominent. The illness lasts usually less than two weeks. It begins suddenly and terminates favorably, except in those children whose resistance is lowered, and in whom general infection and septicemia intervenes or local suppuration takes place.

The frequency of paratyphoid fever in childhood is still largely a matter of conjecture. There have been, however, a number of investigations that would indicate that infection with this group of organisms is by no means uncommon in childhood. Thus Rimpau, among 122 children suffering from gastro-intestinal disease, found that paratyphoid bacillus of the Gärtner group in nine cases; and in one instance the dysentery bacillus of the Flexner type was isolated. Gildemeister and Bärthlein studied 70 infants suffering from gastro-intestinal disease, and isolated dysentery bacilli nine times, paratyphoid bacillus (B), four times, and bacillus enteriditis, once.

Hilgermann, reporting 194 cases of paratyphoid fever, finds it in six instances in children under 11 years; and Rimpau among 528 cases, found none in the first year, 32 between one and four years and 58 between five and nine years. Brenning, among 117 children suffering from intestinal disturbance, found paratyphoid bacillus in 10 instances or in more than 9 per cent. of the cases investigated. Of tehse, three occurred among infants, three among children under three years, and four in children between 9 and 13 years.

In infants the symptoms usually begin suddenly, with diarrhea, vomiting and abdominal pains. There is rather intense thirst and high fever. The fever begins to decline after the third and fourth day, but persists, as a rule, for more than a week. The stools are occasionally very frequent. They may occur every hour, but after a day or two the number rapidly diminishes. The stools contain an excess of mucus and are unusually offensive in odor.

In infants, the duration of the disease is rarely two weeks, though it may last three or four. The most frequent complication is bronchitis, which may be severe and terminate in pneumonia. Jaundice is also not uncommon. A tendency to purulent complications is often marked, the joints being often affected. Cases of unusual severity have been described ending in death by toxemia.

Pathology.—The opportunities for the study of the pathological lesions in paratyphoid fever in infancy and early childhood have been rare. In older children there is the same involvement of the lymphoid structures of the intestines, that has been described in adults suffering with typhoid fever. There is distinctly less tendency to ulceration. In a large proportion of the cases the intestinal lesions are found to affect the cecum or the colon more than the small intestine. In infants apparently, the principal alterations that are noted are an infiltration of the intestinal mucous membrane throughout its entire length, with a dilatation of the blood-vessels and a tendency to hemorrhage and a swelling of the lymph nodules of the small and large intestine. Cloudy swelling is present in liver, spleen, heart muscle and other organs.

The lesions in children are not sufficiently characteristic to distinguish paratyphoid from other bacterial infections of the intestinal tract, without isolation of the causal organism.

Diagnosis.—The statement made in the section upon "Typhoid Fever," namely, that it is impossible by clinical symptoms to differentiate typhoid fever from the infections by paratyphoid organisms, should be repeated here. The isolation of paratyphoid bacilli or positive agglutination reactions is necessary to establish the diagnosis. Not infrequently, infection with both typhoid and paratyphoid organisms may occur in the same patient.

The Different Organisms.—Typhoid, paratyphoid (A) and paratyphoid (B), are said by Dreyer to present marked differences in the readiness in which they are obtained in culture. The typhoid bacillus, and paratyphoid (A) disappear in a few days from the circulating blood. Paratyphoid (B) can be recovered from the stools in more than 75 per cent. of the cases, whereas this is true of typhoid and paratyphoid (A) in only about 20 per cent. of the cases. In practically 10 per cent. of the cases in typhoid and paratyphoid (B), the agglutination gave a positive diagnosis. While in cases of paratyphoid (A) agglutination failed in about 7 per cent. of the cases. In making the tests for paratyphoid organisms, the agglutinating serum should not be diluted in more than 1:50, and at times in thoroughly controlled cases, the agglutination in 1:10 can be used to establish the diagnosis of paratyphoid infection. It will become important then, whenever possible, to investigate bacteriologically and through serum reactions, all cases of fever associated with malaise and diarrhea in young children, especially when the illness occurs in epidemic form. This is especially true when we consider that it has been shown that a considerable proportion of children having had paratyphoid fever even in mild form become in longer or shorter periods, carriers and distributors of the organism.

In young children paratyphoid infection is most apt to be confused with mild typhoid fever on the one hand, and with ileocolitis on the other. As has already been indicated, typhoid fever is exceedingly rare under three years of age and can only be differentiated by the assistance of laboratory methods. When there are symptoms of continuous fever and prostration, the agglutination reaction with all three organisms should be tried, as well as an effort made to obtain the causal organisms from the circulating blood and to identify them by culture in appropriate media.

Ileocolitis is a much more frequent disease, occuring particularly in temperate climates during the warm season. It is associated usually with more diarrhea and the stools contain not only mucus, but blood and pus. The leukocytes are increased in number and the spleen is but moderately enlarged. Mild cases however, on the border line between intestinal indigestion or dyspeptic diarrhea and ileocolitis, may be difficult to distinguish from the rarer infection with the paratyphoid bacilli. Here too the laboratory must furnish our only reliable methods of diagnosis. Other conditions such as malaria and chronic suppurations are to be distinguished from paratyphoid fever in the same manner as has been outlined in the section on typhoid fever.

Prevention.—Paratyphoid organisms, like other members of the enteric group of bacteria, are spread directly or individually from patient to patient. They enter the body through infected water or food, or through direct contact either with a person suffering with paratyphoid fever, or with one who, not having symptoms of the disease is a carrier of the organism.

In young children, contaminated milk is a frequent source of infection. It is safer, therefore, that all milk given to infants, unless it comes from carefully inspected cows, and is handled in the most scrupulous manner, should be scalded or pasteurized before used. This precaution is particularly essential during an epidemic of typhoid or paratyphoid fever. The same rules that have been indicated for the nursing of typhoid cases to prevent the spread of the disease from the stools or urine of the patient to others, should be carried out in the care of paratyphoid cases, no matter how mild the infection seems to be.

The prophylactic use of vaccins against paratyphoid infection has not been as thoroughly tested as in typhoid fever. There is abundant evidence, however, that this form of therapy is equally effective. Paratyphoid vaccin should be given in the same doses and intervals as typhoid vaccin. They can be given in combination, or alternately. The constitutional reaction against paratyphoid (B) vaccin is said to be more severe than that after typhoid and paratyphoid (A).

Treatment.—The treatment of patients suffering from paratyphoid infection differs in no respect from that of those having typhoid fever. During the febrile stage the diet should be fluid and semisolid, of high caloric value, and should be selected so as to be easily digested. Water should be given freely.

Hydrotherapy in the form most adapted to the individual case should be relied upon for the reduction of temperature and the control of nervous symptoms. When the diarrhea is excessive the diet should be much reduced for a short time and an astringent, preferably bismuth in liberal doses, administered. Stimulants are rarely necessary in children except in severe illness. In those cases, they should be given as suggested in typhoid fever. The use of vaccins in the treatment of active disease is still in an experimental stage.

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CHAPTER CXXXIX

TYPHUS FEVER

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Historical Considerations.—Typhus fever probably belongs to the diseases that have been confused with plague during early historic times. It is known as spotted fever, ship fever, jail fever, exanthematic typhus, tabardillo (Mexico), and camp fever. During the nineteenth century it was constantly confused with typhoid fever. The term typhus was first applied to the disease by Boissier de Sauvages in the eighteenth century. The name came into general use through its adoption by Cullen. Typhus has often been mistaken for relapsing fever. The disease is now known to be endemic in northwest India, Mexico, Russia, the Balkans, Japan, China, and no doubt in many other places where poor sanitation prevails and where body lice are common. The conditions resulting from the war have been responsible for terrible epidemics of typhus during the winter of 1919–1920. Poland and the adjacent Russian and former Austrian countries have been through frightful epidemics. Outbreaks occurred in New York in 1881 and 1882, again in 1892 and 1893, and in Philadelphia in 1883. During 1917 the disease was carried into California from Mexico. Cumming[1] reports 24 cases. Doctor Brill[2] first described a disease resembling typhus as occurring in New York in 1896, and since then he has frequently reported cases in that city. It has since been shown by Anderson and Goldberger that Brill's disease and typhus have the same etiology, but the former is much milder in character. The disease has caused terrible havoc on immigrant ships, in jails, or other places where human beings infested with lice are compelled to share quarters under crowded conditions.

Geography.—Typhus fever is primarily a disease of temperate and cold climates, but there have been frequent outbreaks in high altitudes in the tropics. It is a disease of winter and disappears with remarkable regularity upon the approach of warm weather. For instance, in Mexico during the past few years epidemics of 100,000 cases or more have probably occurred. But these promptly subside on the approach of warm spring days. In Mexico the disease prevails almost entirely on the high plateau, most of which is from 4000 to 7000 ft. above sea level. An outbreak occurred in the Philippines in 1913 in the highlands of the Island of Mindanao (altitude about 3000 ft.). It was probably conveyed there by Japanese laborers recently arrived from Japan. Severe epidemics have occurred since the outbreak the European war of 1914. In the early years Serbia probably suffered most. The appalling ravages of typhus in Serbia brought physicians from most of the civilized countries of the world to answer the call to assist in bringing the disease under control. Many physicians and nurses gave up their lives in the cause. Fortunately the advent of spring brought relief. The sanitary measures to destroy vermin in hospitals and other infested human habitations, although employed late, probably had some influence in restricting the ravages of the disease. It has been estimated that over 200, 000 deaths from typhus occurred among soldiers during the recent war. The prevalence of typhus among the Austrian and Russian troops resulted in its being repeatedly carried into Germany. As a defense measure, stations with steam chambers were established between Russia and Germany, and all persons desiring to enter Germany passed through one of these "entlausung" stations. After being bathed and having their effects disinfected, they were given certificates showing that they were free from vermin.

Etiology.—There is still much dispute with regard to the etiology of typhus fever. Plotz[3] isolated an anaërobic organism which he claims is the true etiological factor. He made a serum for the cure of the disease, but the reports so far published are not especially encouraging as to its value. The vaccin made with his organism has also not been effective. Other observers state that organisms similar to those found by Plotz can be recovered with the same technique in certain ascitic fluids. Recently (1920) Mexican health officials reported finding a new organism in the blood of typhus patients. In the past, as in the present, the discovery of the typhus organism has been frequently announced. Klebs[4] found bacilli in 1881. In the same year Mott and Blore[5] described a minute, screw-like, motile organism, as being present in the blood during life, and certain micrococcus bodies in the muscular fibers of the heart after death. In 1891 Hlava[6] described ovoid bodies. In 1892 Thoimot and Calmette[7] saw flagellated bodies. In the three years preceding 1920 the Weil-Felix reaction resulting from the blood of typhus patients being brought in contact with B. proteus (×19) has come to be regarded as of great diagnostic value and the proteus organism is looked upon as part of a mixed infection associated with typhus. Nicolle, Anderson, and Goldberger[8] have experimentally inoculated the disease into monkeys. In 1909 Nicolle[9] reported the transmission of typhus fever by the bite of the body louse (Pediculus vestimenti). This work has been confirmed by Ricketts and Wilder[10] and by Anderson and Goldberger.[11] Anderson, Goldberger, and Foster have also shown that the head louse (Pediculus capitus) may also be concerned in transmitting the infection. The very extensive experience in the great war warrants the deduction that the disease is conveyed entirely by vermin. Body lice are probably the transmitting agents in the great majority of cases, but other vermin, especially the head louse, may at times be responsible. The disease may occur in sporadic form, especially the mild type observed by Brill in New York. Under these circumstances recognition is rather difficult. A mild type has been reported in Manchuria. These mild outbreaks have a very low mortality. In Mexico the disease is usually virulent, and the mortality is often 25 per cent. Ricketts, of the University of Chicago, fell a victim to typhus while carrying on research work in Mexico City. The disease is associated with overcrowding and can usually be traced to conditions in which there is opportunity for persons to exchange body lice. Non-immunes in attendance upon patients are usually attacked. Nurses, doctors, and other attendants are frequent victims. In China, among a very small group of medical men, no less than five lost their lives during the past two years. It is stated[12] that in Ireland, among 1230 physicians attached to institutions, 550 died of the disease.

Bacteriology and Pathology.—The virus may be found in the peripheral blood between the second and fifth days of the fever. The disappearance of the infective agent on the fifth day corresponds with the appearance of the eruption, and it has been held by some authors that the virus leaves the blood and enters the skin. Plotz[13] finds an anaërobic Gram-staining bacillus in the circulating blood, which he claims produces the disease on being inoculated in pure culture into animals.

At autopsy, as a rule, no characteristic lesions are found. The organs present the appearance of an acute infection. There may be some cloudy swellings of the liver and kidneys, and moderate enlargement of the spleen. It is said that if death does not occur until after the second week, there is no enlargement of the spleen. Microscopically the changes are constant and definite. In the arterioles and arterial capillaries, especially those of the skin and central nervous system, there is proliferation and necrosis of the endothelium and intima with the formation of circumscribed perivascular nodules. Typhus gangrene is directly associated with the degeneration of the arteries. Over 50 per cent. of the cases have respiratory complications which are generally responsible for death.

Symptomatology and Course.—The incubation period is variously given from 4 to 21 days. Twelve days is probably a fair average. In a large number of cases studied in Mexico in 1916 the incubation period was apparently 10 days. Among children the incidence is usually not as high as among adults; the mortality is lower and the symptoms are not so severe. The invasion as a rule is abrupt and marked by chills or convulsions, or sometimes by a single rigor that is immediately followed by fever, headache, pain in the back and in the legs. According to Martini[14] rigor is never present in young children and rarely in older children. There is considerable prostration and the patient usually takes to his bed immediately. There is a step-like rise in the temperature until the tenth to the thirteenth day, and then a fall by crisis. The low point is usually reached in 24 hours. A pseudo-crisis sometimes occurs on the eighth or ninth day. The average high point in the temperature is between 104 and 105, but in children it may go as high as 107°F. In the mild form the temperature is much lower. In fatal cases the temperature may reach 108 or 109°F. The tongue is dry, swollen, cracked and crustated with a thick, brown deposit, with red tips and sides. There may be nausea. Vomiting is rare in adults, but may occur in children. The bowels are usually constipated. The nervous system is affected early in the disease. There is usually apathy, drowsiness, and a dull expression. Delirium is common. The eruption appears between the third and fifth days, first upon the abdomen and upper part of the chest, and then upon the extremities and face. Sometimes the eruption can be brought out by placing a constricting band around a limb to impede the venous return. The spots are most difficult to distinguish in the colored races. The eruption usually occurs in three stages. First, erythema. Second, a macular eruption which at the beginning resembles the spots of typhoid, varying from 1 to 10 mm. in diameter and gradually becoming more or less hemorrhagic. This is followed by a petechial eruption. Sometimes the rash appears in the form of rose spots, which may diappear on pressure. In children the rash is often profuse and resembles that of measles. The face is almost never involved. During the second week the general symptoms are much aggravated. As a rule the delirium becomes very intense as the fever reaches the fastigium. Retention of the urine is common. Coma vigil is frequent, in which condition the patient lies with the eyes open, but unconscious. Carphologia is also common.

There is usually an increase in the red cells and hemoglobin. There is always a leukocytosis varying from 14,000 to 50,000 per mil. In uncomplicated cases there may be an increase of 8 per cent. in the polymorphonuclear cells and a decrease in the mononuclears and lymphocytes. A positive Weil-Felix reaction can usually be obtained as early as the third day. In severe cases there may be hypostatic congestion of the lungs. The heart also frequently becomes feeble and there are signs of myocarditis. It should always be remembered that there may be any number of varieties of the disease, varying from very mild cases to those of the more virulent type.

Complications.—Sequelæ.—Bronchial pneumonia is the most common complication. In some epidemics gangrene of the toes, hands, ears, or nose, may occur. Children more often suffer with noma or cancrumoris. Paralyses due to post-febrile neuritis are infrequent.

Prognosis.—The mortality among adults ranges in different epidemics from 12 to 20 per cent. and considerably less in children. After middle age the mortality rapidly rises and in some epidemics reaches 50 per cent. Death usually occurs during the second week. One attack of the disease seems to confer permanent immunity.

Diagnosis.—During an epidemic the diagnosis presents few difficulties. Isolated cases, especially mild cases such as described by Brill, may be difficult to distinguish from typhoid fever. The positive Widal reaction and blood cultures in the latter disease will leave no doubt after the first week. In children the onset is often similar to that in typhoid, but the persistent headache and nose bleed are absent. At times it is most difficult, if not impossible, for the most expert clinician to make a diagnosis. Malignant malaria may simulate typhus, but this disease can be readily differentiated by the plasmodia in the blood. At the termination of the fever cycle the fall by crisis in typhus and by lysis in typhoid is an important distinguishing point. The more positive signs are the leukocytosis, associated with the rash, and extreme nervous prostration. Relapsing fever often occurs coincidently, but can be readily distinguished from typhus by the spirilla in the blood. Koplik's spots and the coryza will readily exclude measles.

Treatment.—In general the treatment of typhus is in every respect similar to that of typhoid. Hydrotherapy in the form of cold sponging or tub baths to keep down the temperature, when it reaches 102 or more, should be regularly employed. This will probably relieve the nervous symptoms as effectively as it does in typhoid fever. It is well to begin the treatment with fractional doses of $\frac{1}{10}$ gr. of calomel every hour until bowel action has been obtained, and this should be followed by several teaspoonfuls of magnesium sulphate. The heart must be carefully watched, and if it weakens, heart stimulants like strychnine or digitalis should be administered. Some authors have used serum taken from cases which have recently had typhus fever, and in those who are very ill it is believed that its intravenous use is a procedure well worth trying. Water should be given freely. The diet should be liquid until the fall in temperature. The patient should be placed preferably in a well-lighted, airy room, or treated on a verandah or in a tent, if climatic conditions permit.

Prophylaxis.—The researches of Nicolle, Anderson, and Goldberger, in which the transmission of the disease by body lice was definitely proved, have made it possible to place the prophylactic measures upon a sound scientific basis. The pediculus vestimentorum being so definitely concerned in the transmission of the disease, it is apparent why overcrowded, filthy, and unhygienic surroundings are so intimately associated with typhus. The prevention of typhus, therefore, resolves itself into the destruction of the body louse. This insect does not travel far, except as it may be carried on the bodies of people or in baggage. In all preventive measures it is important not only to destroy the body lice, but also their eggs. The patient's clothes should be removed and thoroughly boiled or treated with steam under pressure. Strong chemical solutions cannot be depended upon to kill the lice and their eggs. The bodies of typhus patients and others who have become infected with lice should be washed with gasoline. This is necessary because body lice frequently bury themselves in the skin, and an oil removing substance like gasoline or ether is essential to their removal. This should be followed immediately with a hot bath. It is also advisable to use a very strong alkaline soap and for this purpose the so-called sea water soap, when used with fresh water, is of considerable advantage. For hairy parts of the body a paste can be applied, composed of two parts strontium sulphate and one part each of zinc oxide and talc powder. This can be removed in 15 minutes. Care must be taken to protect the eyes. Those who come in contact with typhus patients, especially doctors and nurses, should take all possible precautions against being bitten by body lice. Fairly good prophylaxis is possible by using special gowns of white cotton and boots, the openings of which are tightly closed, especially at the neck, wrists, and tops of the boots. This may be accomplished with elastic material. Insect powders or solutions are of some value when applied to the body and clothing. Powdered naphthalene is fairly efficient in preventing the lice from entering or living in personal effects. Eucalyptus, camphor, oil of citronella, ordinary kerosene, and powders composed of starch and camphor, are all more or less used. The clothing of all attendants should be frequently changed and thoroughly boiled before being used again. Whenever effective measures for the destruction of body vermin are carried out, the disease rapidly disappears.

To prevent typhus from being carried into a country, all persons from infected regions should be thoroughly bathed and all their textile effects should be disinfected with steam under pressure in a modern steam chamber. When no steam chamber is available, effects may be boiled or steam used in a tight compartment, as, for instance, a refrigerator car.

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CHAPTER CXL

ACUTE RHEUMATIC FEVER IN CHILDREN

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Etiology.—Numerous theories have been advanced in explanation of the occurrence of acute rheumatic fever. In the light of recent bacteriological studies, many of these explanations must be looked upon as nothing more than predisposing conditions, leading to an acute infection, due to microörganisms, which gain an entrance into the body through the oral or nasal cavities, and by metastasis develop lesions usually manifested by focal and sometimes by generalized infections with septicemia.

It is difficult to credit the view of the bacterial origin of the disease to any one investigator, for authorities are not yet agreed as to the nature of the specific organism.

As early as 1887 Mantle[1] published a paper in which he claimed to have demonstrated bacteria in joint fluid and blood of rheumatic cases. Later various continental investigators, especially Wasserman, reported similar findings.

The greatest impetus to the theory of bacterial infection was given by the elaborate and painstaking researches of Poynton and Paine. They isolated a small micrococcus 0.5μ in diameter growing in pairs or short chains, which they called the diplococcus rheumaticus, and which they demonstrated in a large proportion of cases examined. This organism was isolated in pure culture, and with it characteristic lesions of rheumatic fever were produced in animals. They produced experimentally all forms of arthritis, including the chronic rheumatoid type with severe destruction of bone and cartilage and muscular atrophy. In some cases the diplococcus produced simple endocarditis, in others a malignant type of infection.[3] In all cases they recovered the organisms in the inoculated animals.

Many other investigators have been able partly to confirm the findings of Poynton and Paine but negative cultures from joint and blood were so frequent as to throw some doubt upon the specific nature of the diplococcus rheumaticus.

In 1913 E. C. Rosenow[4, 5, 6, 7, 8] following a specially developed technique obtained positive cultures from affected joints and blood

Rosenow had found that oxygen pressure plays an important part in the transmutation of pneumococci and streptococci. He conceived the idea that the bacteria in rheumatic cases might be so sensitive to oxygen that the many negative cultures, in a disease so suggestive of infectivity clinically, might be due to failure to supply and maintain proper oxygen tension in the culture media. His technique[7] provides therefore a culture tube in which aërobic conditions exist at the surface, and anaërobic at the bottom; in between, the inoculated material is exposed to a gradient of oxygen tensions. By use of this method he secured pure cultures of streptococci from joint fluid in 16 out of 19 cases of acute rheumatism and from the blood in five out of eight cases. In two cases in this series the same or very similar organisms were found in the tonsils. Experimental inoculation in animals showed that the organisms were of relatively low virulence as compared with other strains of streptococci. He produced repeatedly multiple non-suppurating arthritis, endocarditis, pericarditis and myocarditis in the same animal. By animal passage and other means these strains were converted into typical hemolytic streptococci and pneumococci.[5]

One strain in transition developed an affinity for myocardial and skeletal muscle and kidney tissue and lost its affinity for joint tissue and for endocardium and pericardium.[4] In other words, his work strongly suggests that streptococci from various diseases have a striking affinity or tropism for the organs or tissues from which they are isolated. Streptococci of low virulence but highly sensitive to oxygen, were found to produce lesions in tissues whose blood supply and therefore whose oxygen and food requirements are low, such as valves, tendinous portions of muscles and structures about joints. Streptococci of greater virulence produced lesions in tissues whose blood supply and oxygen requirements are high, such as lungs and kidneys. It would appear as if the tissues for which a given strain shows elective affinity take the bacteria out of the circulation as if by magnet absorption.[6]

On the other hand, bacteria of low virulence such as are found in chronic foci of infection, tend to make the soil for their own growth more favorable.[6]

Since different bacteria may acquire simultaneously affinity for the same tissue, diseases which resemble each other more or less closely, such as the different forms of arthritis, may be due to bacteria of different species, each having elective affinity for the particular structures involved.

The tendency to localize electively within a limited range (monotropism) is most highly developed in the relatively non-virulent strains isolated from chronic lesions. Rosenow calls attention to the bearing the above observations of his may have upon the specific treatment of these bacterial infections, for the injection of a streptococcus vaccin or autostreptococcus serum, without regard to the tropic condition of the infecting strain or the one used in their preparation, is far from an exact method of treatment.[6]

Bloomfield,[4] following Rosenow's special technique, has isolated from the blood and lymph-nodes, in cases of arthritis, streptococci apparently identical with those described by Rosenow. It appears to be well established therefore that streptococci in pure cultures can be isolated from joint fluid and blood in a large proportion of cases of acute rheumatism. The strains, however, differ in one respect or another from streptococcus viridans and streptococcus hemolyticus. They vary in virulence and tend to change their properties on cultivation outside the body and possibly may undergo similar changes within the body. In fact Rosenow's experiments on mutation lead him to believe that he can convert the rheumatic strains of streptococcus into other members of the streptococcus group and *vice versa.* These cultural peculiarities may be found to explain the differences between the types of organisms isolated by various investigators.[4,5]

Portal of Entry.—The oral and nasal cavities must be looked upon as the probable portal of entry of the primary rheumatic infection, the greatest importance being attached to the tonsils. In very many cases of rheumatic fever the diseased condition of the tonsil is apparent. Unfortunately foci of disease may be concealed deep within the tonsillar crypts, and neither their size nor external appearance suggests a latent danger. Other sources of infection such as dental caries, pyorrhea and necrosis of the jaws and nasal structures, diseased adenoids and inflammations of the accessory sinuses, are less frequent but possible portals of entry.

Brilliant results are not infrequently met with, especially in first attacks of rheumatic fever, upon removal of the focus of infection when detected in the regions mentioned. Operative measures are however often disappointing and no relief of symptoms follows. This may simply mean that other foci of infection may be too small to be detected or may be present in inaccessible regions; or that living bacteria in a metastatic condition may continue to excite the inflammatory process independently of the focal source.[7] The exact part played by tonsils, dental caries and nasal infections in causing the primary rheumatic infection, their relation to exacerbations and reinfections and their relative importance in the etiology will probably never be determined on the basis of clinical investigations alone. Bacteriological investigations along the lines followed by Rosenow offer the best hope of a solution to many puzzling questions and differences of opinion among competent observers.

It is probable that we shall come to look upon acute rheumatic fever as upon such diseases as pneumonia. The latter is due to a specific organism, the pneumococcus in the great majority of cases, but exceptionally to other bacteria. So with acute rheumatism, we are inclined more and more to believe in a specific streptococcus or diplococcus as the chief primary causative agent, but we must admit other forms of infective arthritis with cardiac infections. These principal symptoms occur in many acute specific infectious diseases, such as scarlet fever, small-pox, typhoid, dysentery, gonorrhea, syphilis and tuberculosis. Moreover the relation of such conditions as Still's disease and the rheumatoid arthropathies to the specific rheumatic streptococcus or diplococcus is by no means settled.

Pathology.—The most characteristic lesion of acute rheumatic fever is the submiliary nodule which is found in the various tissues affected. The nodules consist of large spindle-shaped cells situated in the intermuscular trabeculæ of connective tissue. They resemble fibroblasts and are multinuclear, and are surrounded by plasma cells and mononuclear leukocytes. They do not constitute a specific test of the disease, but several inuestigators have reproduced them in animal inoculations.[2]

Poynton describes several types of lesions: (1) Simple type, illustrated by arthritis, in which there is microscopically dilatation and sometimes rupture of the blood capillaries with marked swelling of the neighboring connective tissue. If the infection is mild, the inflammation subsides, leaving no mark; if it is severe, necrosis of the tissue may occur, with subsequent scar formation, as in disease of the mitral valve. When the foci of infection occur in the subendothelial tissue of serous membranes, a rapid exudation of sero-fibrinous fluid takes place into the serous cavities. The fluid is never purulent. The difficulty of finding bacteria in these exudates has been explained on the ground that the microörganisms are located in the subendothelial tissue, and at first the endothelium serves as a bar to their escape into the serous cavity. When later they pass this barrier owing to the destruction of the protective endothelium they are attacked by the leukocytes and destroyed by them. On the other hand, the explanation may be due to cultural peculiarities of the organism as pointed out by Rosenow, who believes that by his special technique he can isolate the infecting organism in a great majority of cases and in practically all affected tissues. At one time or another the diplococcus, rheumaticus and similar organisms described as a diplococcus, streptococcus or micrococcus, of different investigators, according to the individual technique have been demonstrated in the endocardium, pericardium, the pluræ, peritoneum, pia mater, synovial membranes, nodules, lungs, urine and blood.

2. The Fibroid Type.—This is shown best in the lesions of mitral stenosis, curiously most common in females. Very little necrosis occurs in this type and the sclerosis is the result of a very gradual but persistent process.

3. The Malignant Type.—Here the microörganisms are not destroyed but multiply in the tissues and are disseminated in the blood stream. The vegetations contain large numbers of bacteria but are very minute.

4. Lesions Produced by Rheumatic Toxins.—Fatty degeneration of the tissues is the chief manifestation of these agents. It is especially well seen in the cardiac muscle and in the convoluted tubules of the kidneys. In the nervous system vascular and inflammatory, with destructive secondary changes have been demonstrated, with morphological changes in the nerve cells. Diplococci and the submiliary nodules have been found in the pia mater.

Inflammatory changes have been shown to exist in the intima directly beneath the lining endothelium of arteries, veins and capillaries.

In subacute lesions perivascular fibrosis occurs which by contraction of the lumen of the smaller blood-vessels probably interferes with the circulation in tissues supplied by them. Phlebitis with venous thrombosis occurred in seven of Poynton's cases.

Arthritic Lesions.—Arthritic lesions can be readily induced in animal experimentation by inoculation with the diplococcus rheumaticus and similar microörganisms. There is first a deposition of bacteria in the subendothelial connective tissue of the synovial membrane with extensive inflammatory reactions. This is followed by invasion of the tissue with leukocytes which destroy the microörganisms. An exudation of a clear or blood-stained and later fibrinous fluid follows. The capsular tissue becomes swollen and gelatinous. According to Poynton, even lesions of chronic osteoarthritis can be produced by the diplococcus rheumaticus by inoculations into rabbits.

The tendons show inflammatory changes along their sheaths with gangliform swellings and adhesions. Periosteal nodes appear in the periosteum.

The subcutaneous nodules so characteristic of the disease in England have also been produced by experimental inoculations.[9] These result from the local deposit of bacteria and are associated with swelling of the subcutaneous tissue, dilatation of the blood-vessels, exudation and necrosis. Fibroid changes may occur in these necrotic areas. In size they vary from a pin head to that of an almond and are most easily seen if the skin overlying them is stretched and a light thrown on it obliquely. They are most common over bony prominences and tendons. It is possible that stiff necks, pleurodynia, and lumbago may be muscular rheumatism due to the occurrence of similar localized connective tissue inflammatory nodules in the muscular tissue.

Predisposing Causes of Infection.—Under this heading one is now inclined to include most of the causes which formerly were considered direct and primary factors in the production of acute articular rheumatism. Very often the onset of the disease definitely follows a severe exposure to cold or wet weather, to damp, unhygienic surroundings, and to sudden unseasonable changes of weather. As a matter of fact, any cause operating to lower a child's power of resistance may lay the groundwork for bacterial invasion of the tissues. Any previous disease attacking the protective barriers at the protals of entry, such as tonsils, teeth, gums and nasal sinuses, increases the possibility of providing the foci of the specific bacterium. With these two factors assured, the child who has been underfed, improperly clothed, whose vitality has been weakened by previous diseases in rapid succession or by undue exposure becomes a ready victim to rheumatic infections. Undoubtedly the disease is most frequently seen among the poor. It is however not uncommon for the well to do and even the rich to overlook foci of infection in the oral and nasal cavities and acute rheumatic fever is by no means exclusively a poor man's disease.

Heredity.—Heredity is a decided factor in some cases, as rheumatic disease may occur in several generations in an increasing ratio. Holt secured a rheumatic family history in two-thirds of his cases. There is of course no direct inheritance of the disease but it is probable that the rheumatic child of rheumatic parents has inherited a quality of tissue for which the microörganisms of rheumatism have a definite electivity.

Age.—Symptoms of rheumatic fever as seen in adults are uncommon in the early years of childhood, so that the frequency of its occurrence in children was not appreciated until the English physicians, especially Cheadle, enlarged our views of the varied manifestations of the disease in early life. It is however exceedingly rare in infancy, and is uncommon under four or five years. Infantile scorbutus may be confused with it by inexperienced physicians. Holt has seen one typical case with multiple joint lesions in a nursing infant, but such cases are exceptional. After the age of five years, acute rheumatism becomes one of the most frequent and serious diseases of childhood, owing to its predilection to attack the heart muscle, endocardium and valves. Its great tendency to recur and with each recurrence to add to the cardiac lesions, eventually leads to the most serious cases of chronic carditis.

The seasons play little part in the etiology, though the incidence of the disease is increased in the spring. In childhood females are more frequently attacked than males and are more susceptible to chorea.

Chemical intoxications were at one time thought to be the etiologic factor, and much importance was attached to the theory that acids, especially lactic, formic and uric, were primary causes. The pungent acid sweats, the highly acid condition of the urine, more common in adults than in children, added weight to this theory. These conditions, now, are looked upon as results rather than causes of the disease. Injuries to the joints may precede the onset of rheumatic symptoms. In such cases trauma must be looked upon simply as a localizing cause in one who has been previously infected and still harbors latent foci of infection which become active under the stimulus of a sudden lowering of local resistance.

General and Articular Manifestations.—The manifestations of acute rheumatic fever in children depend upon two factors, first the local effects of the growth of organisms in the various foci of infection, and, second, the results of the toxins after absorption into the blood circulation. These symptoms show a striking difference according to age. In adults the manifestations seem to be due mainly to toxemia, while in children focal symptoms predominate. A reasonable theory to explain this difference would be in the hypothesis that in adults the chief site of the multiplication of the organisms and the manufacture of the toxins is in the blood itself, while in children it is in the focal lesions outside the blood stream. When the toxins are absorbed into the circulation from outside they would naturally be less in amount, and would produce less violent symptoms.

Rosenow's theory of high and low virulence of the infecting organism and the affinity or tropism for different organs and tissues which it develops within the body is a still more plausible explanation of the variation in symptomatology in adults and young children. It is conceivable that the quality of tissue, as influenced by the age of the individual, may in some way influence this phenomenon of tropism.

The symptoms complex of acute rheumatic fever, that is, high fever of sudden onset, severe inflammation of successive joints, showing pain, swelling, redness, and tenderness, profuse acid sweats and severe nervous manifestations, which characterize the adult type, are seldom seen in children under 10 years of age. The disease is less acute, often with a period of mild evanescent symptoms, suggesting a prodromal stage. There is frequently a history of acute tonsillitis of varying degree of severity followed by a low range of temperature with fleeting, indefinite pains by no means always referred to the joints. When the joints are involved there is seldom redness or extreme tenderness, and the pain and swelling yield readily to salicylates and local applications. Pain and moderate degree of stiffness are often alone present. Successive joints are apt to be involved, but the local symptoms often pass in a few days. Sometimes the course is measured by hours. The knees and ankles, as in adults, are most frequently involved, more rarely the elbows and small joints of wrists and ankles, and sometimes those of the cervial vertebræ.

The fever rarely exceeds 102.5°F. and drops with or without treatment to a low range varying from normal to 100.5°F. which persists often long after all objective and subjective symptoms have passed. The pulse rises with the fever in the acute stage, dropping quickly to normal with the defervescence of temperature unless the heart becomes infected. A persistent high pulse rate is one of the most suspicious indications of cardiac involvement, even with negative auscultation findings, and is of the greatest value in determining the activity of the infection and the rapidity with which one may relax the rigid insistence upon complete rest in bed which should be prescribed with the first evidences of the disease.

Profuse acid perspiration may occur in older children, in whom other symptoms follow the adult type, but is absent in the usual run of cases in early life.

The nervous manifestations may be many, but are not distinctive of rheumatism. Emotional hyper-sensitiveness, mental impairment, as in the severe cases of chorea, talking in sleep, somnambulism, night terrors, headache, epigastric pain, and disturbed digestion, either constipation or mild diarrhea are possible accompaniments of the disease.

As the symptoms progress the child may become pale and pasty, and if there is much pain the countenance is anxious or distressed. A mild leukocytosis develops and varying degrees of secondary anemia are invariably noted if the case is at all prolonged. Erythema multiforme is frequently seen in all its varied manifestations.

English writers lay great emphasis upon the occurrence of subcutaneous nodules, but in this country, for some reason not explained, they are rarely seen. When they do occur they are found in the tissues over bony prominences, but are not attached to the periosteum, unless the subcutaneous tissue is in close contact with the periosteum, as in the skull or patella. These nodules are not to be confused with the rheumatic nodes seen in the more chronic cases, which are periosteal growths occurring over the shafts of the long bones. They consist of fibro-plastic cells situated in the subcutaneous tissue of the scalp and over the sheaths of the tendons, especially those of the flexors of the wrists. As the disease recedes they are converted into fibrous tissue. They occur in successive crops, each node varying from a very small kernel to a small pea-sized tumor. They may be few or very many in number. As long as they are present, the infection must be considered active, and they are, therefore, of much importance in questions relating to prognosis and treatment.

Pleurisy and pneumonia are not commonly met with as complications, but are more frequent in children than in adults.

Inflammations of other serous membranes, such as the periosteum and pia, were more frequently attributed to rheumatism in the past than now.

There is reason to believe that there is a close connection between purpura and rheumatic infections, but the exact relation of the two conditions cannot be definitely stated. The disease, *rheumatic purpura*, is distinct from other forms of purpura, but does not come into the scope of this article.

A considerable variety of cutaneous eruptions may be seen in the course of a large series of cases of acute rheumatic fever. There is nothing distinctive about these affections which makes them in any way diagnostic or different from similar skin manifestations seen in many other infections. *Sudamina* and intertrigo frequently occur, the result of sweating and fever. Urticaria and the many forms of erythema may be seen. These, undoubtedly, are dependent on the absorption of poisonous material, which is either directly of bacterial origin or the result of the formation in the affected tissues of new substances incited by the action of the toxins formed by the growth of the microörganisms.

The relation of erythema nodosum to rheumatism is suggested by its not infrequent association with it and occasionally by its occurrence as a primary condition which is succeeded by arthritis and endocarditis. In England the peculiar subcutaneous nodules have also been noted. The majority of cases, however, run their course without any of these rheumatic symptoms. There is no strong scientific evidence to connect the two conditions etiologically.

Cardiac Manifestations.—Cardiac involvement generally appears at the end of the first week, but may precede any localization of the infection in the joints; in fact it may be coincident with the onset of the earliest symptoms. Acute endocarditis or pericarditis in a child, occurring as a primary condition, must be looked upon as probably of rheumatic origin. Since young children seldom complain of localized pain and palpitation, it may happen that the evanescent articular symptoms may be entirely overlooked, and the first symptoms for which medical treatment is sought are those of mitral insufficiency.

The course and serious aspect of acute rheumatic fever depend almost entirely upon the degree and severity of the cardiac involvement. This is not to be looked upon as a complication but as a cardinal symptom, vastly more important than the articular or any other manifestations of the disease. There is no form of cardiac infection which may not be met with. Pericarditis, endocarditis, acute and chronic, myocarditis, valvular disease, and functional valvular conditions are possible results of the rheumatic infections.

The hearts of children escape injury much less frequently than those of adults, but permanent heart disease does not invariably follow definite signs of involvement of the heart. A murmur or even a pericardial rub may occur in the course of an attack of acute rheumatic fever, but may disappear completely and leave no sign of permanent impairment. There is, however, a strong tendency to recurrence of the rheumatic condition, and with each one the heart seems to show a greater susceptibility to infection, and seldom escapes serious injury after several attacks. A permanent murmur implies defective valvular action resulting from stenosis or incompetency; but one's judgment as to the extent to which the child's health is impaired depends more upon the evidence as to how far the myocardium has been damaged than upon the fact that the valvular defect is permanent.

There is no direct relation between the incidence of carditis and the severity of the rheumatic attack. Cases showing only mild degrees of arthritis and slight sore throat with moderate temperatures are quite as likely to give rise to serious involvement of the heart as those which start with more acute and pronounced symptoms. In children particularly the great majority of cases of acute and chronic heart disease in hospital wards are of rheumatic origin.

Acute Endocarditis.—The early recognition of involvement of the endo- or pericardium is of the utmost importance for the future health, and even the life of the child may depend upon the insistence of immediate and prolonged rest in bed. Immobility of the joints unquestionably has much to do with the rapid control of articular symptoms. Everything which can be done to lessen the work of the heart in a similar way influences favorably the course of the inflammation. Slight irregularity of heart sounds, a persistently increased pulse-rate, a vague sense of precordial discomfort, a modified or changed character of the first sound, a reduplication of the second sound at the apex, a displacement of the apex beat all may point to the early development of endocarditis or myocarditis. To wait for the detection of numerous indications of the particular affection of valves often involves the loss of valuable time in treatment. The important point to recognize is not so much the nature of the valvular lesion, as the fact that the infection has been localized in the heart.

Sometimes the onset is severe and the infection fulminating, leading to a general carditis with fatal termination. In other cases it is insidious and the cardiac symptoms are as transitory as the arthritis. In severe cases dilatation of the heart is often very rapid, and the symptoms urgent. Dyspnea, pallor, vomiting, and delirium are associated with a rapid, feeble, irregular heart. The heart sounds are weak, a mitral *regurgitant* murmur is heard and the end comes by syncope. Such conditions probably represent a sudden damage to the cardiac nerves with loss of muscle tone. In adults the investigations of the heart muscle with the electrocardiograph has added much precise knowledge as to the nature of the myocardial lesions, but in children the results have been much more difficult to obtain and are less constant and significant.

A systolic murmur at the apex may not mean a diseased mitral valve. It may be simply a relative incompetence due to the action of the rheumatic toxins upon the heart muscle, and may completely disappear with prolonged rest and intelligent treatment. In fatal cases, however, the mitral valve is seldom found undamaged. In 250 cases reported by Poynton, Agassiz, and Taylor[10] the aortic valve was, in addition to the mitral valve, affected in 102 cases, the tricuspid in 78 cases, and the pulmonary valve in six cases. Evidence of pericardial involvement is present in a considerable portion of cases. The valves are swollen and inflamed—with beads of fibrin from the circulating blood deposited upon small ulcerated surfaces, forming the typical vegetations. These form on the proximal surfaces of the valves at a distance from the free margin. Healing occurs by fibrosis, with resulting deformity. Permanent incompetence and stenosis result. Recurrent attacks render the conditions worse. Hypertrophy and dilatation occur and in time end in broken compensation with the usual train of symptoms. Myocarditis is almost invariably present to a greater or less degree in all cases of endocarditis.

Acute pericarditis may occur alone or in conjunction with valvular disease. It is less common than endocarditis, but is more frequent in childhood than in adult life and is the most frequent cause of death in rheumatic fever. This is apt to occur a week or so after the defervescence of the fever and articular symptoms, and is more common in boys than girls. Both parietal and visceral layers become covered with a thick layer of lymph, which becomes roughened by the constant heart action. The friction of the diseased surfaces causes the characteristic to-and-fro murmur at the base of the heart, often with severe precordial pain. In other children the discomfort is unaccountably slight. Adhesions may form with obliteration of the heart sounds, or the accumulation of a sero-fibrinous exudate in the pericardial sac may accomplish the same result. In such cases the characteristic signs of fluid are easily detected, that is, marked increase in the area of cardiac dulness, obliteration of the normal acute right cardio-hepatic angle, and muffled heart sounds. With the re-absorption of the fluid the friction rub usually reappears until obliterated by the permanent adhesions between visceral and parietal layers of the pericardium.

Dilatation of the heart contributes largely to the very greatly increased area of cardiac dulness. Unfavorable symptoms are delirium, restlessness, vomiting, and livid color, but death rarely occurs in the first attack.

Persistent and progressive pericarditis may occur in a subacute form over a period of months, giving rise to the chronic adhesive type so frequently found in children. Very dense pericardial adhesions form. There may be an associated mediastinitis, pleuritis and even peritonitis. Poynton believes that multiple serositis is simply a manifestation of this type of rheumatism.

Lesions of the Mitral Valve.—A soft systolic murmur heard at the apex and transmitted into the axilla, indicative of regurgitation, is the first result of the infection. With it is generally a prolongation of the first sound and persistent reduplication of the second sound at the apex, pointing to a thickening or stenosis of the mitral segments. Sometimes a to-and-fro murmur is heard over the apex. In the subacute types of infection mitral stenosis is especially liable to develop in children. This is particularly true of girls. The blowing regurgitant murmur is followed by a sharp first sound, or, if more advanced, by a rumbling diastolic or presystolic murmur, with a palpable presystolic thrill. Stenosis without regurgitation is extremely rare.

Lesions of the Aortic Valve.—The aortic second sound becomes less distinct while a soft diastolic murmur and sometimes a transient systolic murmur is heard just to the left of and over the sternum. There is usually considerable cardiac excitement with forcible arterial pulsation. Aortic regurgitation is often combined with mitral disease, and the involvement of both valves may be detected by auscultation. If the mitral lesion is severe, there is apt to be associated congestion of the blood vessels of the lips and cheeks with slight puffiness of the face simulating renal disease.

Malignant Endocarditis.—Every gradation from simple endocarditis to malignant endocarditis may occur, but the severe malignant type is rare in children. Severely septic types occur and last for weeks with eventual temporary convalescence, but always with a badly damaged heart which generally succumbs to the next recurrence of rheumatic fever. This type is suggested by the persistent irregular fever of a septic type, much cardiac excitement, with severe anemia, sweating and purpura. This type of endocarditis has been produced experimentally in animals by Poynton and Paine[2] by inoculations with the diplococcus rheumaticus. It probably requires secondary causes to aid in its production, such as previously damaged valves, extremely unhygienic surroundings, and severe anemias. Some cases run a protracted course for months; others prove rapidly fatal. It is often associated with malignant pericarditis.

Blood Changes.—During the active stage of rheumatic fever, there is a rapid development of secondary anemia, with moderate leukocytosis. In malignant cases marked hemolysis may occur. The anemia may reach such a degree of severity as to interfere seriously with the course of the disease, contributing largely to a fatal ending.

Cerebral Rheumatism.—The relation between acute rheumatic fever and certain manifestations of disease of the nervous system has long been recognized. Some writers have limited the term, "Cerebral rheumatism," to the severe form of involvement of the nervous system characterized by hyperpyrexia, coma, and delirium. This type is seen more frequently in adults, especially in cases of alcoholism. It is more common in males. The onset occurs in the third or fourth week of the infection, coming on abruptly with headache, delirium, insomnia, and vomiting. Spasmodic twitching and irregular breathing follow. The patient passes into a state of coma of varying degrees of severity. The temperature rapidly rises to extreme heights, 110 and 111°F. being recorded, but may not exceed 104°F. if salicylate treatment and hydrotherapy is instituted early and vigorously. In rapidly fulminating cases, or even in the severer cases not ending fatally, marked meningismus is present, and sometimes generalized clonic convulsions. Fortunately, it is very rare to see this type in children.

Chorea.—The relationship between chorea and acute rheumatic fever is very close. It may be looked upon as a form of cerebral rheumatism, but the explanation of its varied manifestations is made difficult by the infrequency of opportunities to study the tissues in fatal cases of chorea. Poynton and Paine have cultivated the diplococcus rheumaticus from the cerebrospinal fluid in three cases of rheumatic chorea, and from the cultures obtained have produced in rabbits arthritis, endocarditis, and pericarditis.[11] Poynton and Holmes, in three fatal cases of chorea, found characteristic changes in the nerve cells. These results strongly suggest that the infectious agent of chorea may produce an inflammation of the meninges, brain, and cord, and by its lesions and toxins be the direct cause of the nervous phenomena.

It is by no means determined, however, that all cases of chorea are due to the microörganism causing rheumatic fever. As other bacteria may produce arthritis and carditis, so chorea may have a number of etiological factors. In children, however, chorea and rheumatism are associated in a very large proportion of cases. Holt states than in his own cases over 50 per cent. of the choreas have given unmistakable evidence of rheumatic diathesis. The proportion of cases will depend very largely upon what one admits as evidence of rheumatic fever. If cases of acute endocarditis without arthritis, and those of articular pain and joint stiffness, but without swelling, are classed as rheumatic, the percentages of cases of chorea showing rheumatic symptoms may be rated very high. Also the number of cases of acute rheumatic fever showing sooner or later in the course of the disease symptoms of chorea is very large. Here the proportion, again, depends largely upon the individual point of view of how much of a manifestation of nervous incoördination justifies the diagnosis of chorea. The exact relationship of the two conditions will not be determined until their bacteriology has been more fully developed.

Between cerebral rheumatism and chorea, as two extremes, many intermediate types of nervous manifestations are seen, differences dependent upon variations in the strain or virulence of the infecting organism, or in the localization or intensity of the toxemia.

Unusual Complications.—Peritonitis and appendicitis have both been produced experimentally by inoculation with the diplococcus rheumaticus. In fatal cases of rheumatic fever, the organism has been found in the lesions of chronic peritonitis, about the liver and spleen. It is also freely excreted in the urine of affected patients and in rare instances nephritis has been produced in inoculation experiments.

Acute nephritis as a complication of acute rheumatic fever is probably more common than is supposed. Systematic and careful examination of the urine and sediment often show mild degrees of renal irritation. In malignant cases, of course, severe hematuria and nephritis occur. Some of these cases develop into chronic nephritis. It is probable that many cases in children of chronic renal disease have their origin in a previous mild or unsuspected rheumatic infection.

Mastitis has been observed by Still in childhood. Thyroiditis, parotitis and lymphadenitis and erythematous and phlyctenular conjunctivitis and acute iridocyclitis occur rarely in children.

Muscular Atrophy.—Diffuse wasting of muscles throughout the body may occur in prolonged cases of rheumatic fever, as in any other condition in which the patient is confined to the bed for long weeks. Aside from this, however, there is a localized arthritic muscular atrophy which may accompany any inflammatory disease of a joint, acute or chronic. The muscles of the shoulders, knees, hips, elbows and fingers are most likely to show this change. The atrophy is sometimes sudden in onset and reaches its maximum in a week or 10 days, if the arthritis is of acute onset. If the rheumatic infection is subacute or chronic, the muscular wasting is gradual. The muscles which are most susceptible to this atrophic process are those which are involved in the extension of the joint, such as the quadriceps in arthritis of the knee, the gluteal in case of the hip joint, the deltoid in the shoulder joint, the triceps in the elbow, and the interossii in the fingers. The muscle is affected throughout its whole length. It is seldom tender, shows no fibrillary tremors and only slight diminution in its electrical excitability to faradism and galvanism. The condition, therefore, differs somewhat from the atrophy occurring in neuritis and poliomyelitis, in that there is no reaction of degeneration. Cutaneous anesthesia and tingling do not occur in this form of arthritic muscular atrophy, unless the inflammatory process spreads from the joint into adjacent nerve fibers, which does not often happen.

Rheumatic neuromyositis differs from arthritic muscular atrophy in that pain is referred to the muscles themselves and is associated with cutaneous pain or hyperesthesia, but without pain or rigidity in the joints. Muscles of the limbs, vertebral column and scalp are not commonly affected, although any voluntary muscles of the body may be affected. The condition is less frequent in children than in adults.

Diagnosis.—The diagnosis of acute rheumatic fever in childhood is often overlooked, owing to the mildness of its initial symptoms and the frequent absence of the typical arthritis seen in adults. The child's complaints are often vague. He appears not well, may complain of headache or lassitude and indefinite transitory pains, by no means definitely localized in the joints. They pass as "growing pains" and the true nature of the infection is not appreciated until with the fever there develop symptoms pointing to either arthritis, chorea, or endocarditis.

The careful physician will make a searching examination of the oral and nasal cavities in every child he sees. Dental caries, stomatitis, enlarged ragged tonsils, present in so large a percentage of children in routine hospital work, should suggest a child susceptible to rheumatic infections, whether other symptoms are present or not. A moderate, persistent elevation of temperature—99.5 to 100.5°F.—not otherwise explained, may also be looked upon as suspiciously rheumatic. Frequent attacks of sore throat and colds, indicative of lowered local resistance from functional inactivity of the adenoid and tonsillar protective structures, while not necessarily rheumatic, should be looked upon as danger signals, and possible favorable portals of entry for generalized infections. Subcutaneous nodules should be searched for in every suspicious case, for they are of great diagnostic importance.

Differential Diagnosis.—The diagnosis of acute rheumatic fever in a child under 18 months may be looked upon as probably an error. The condition most frequently overlooked is **infantile scorbutus,** which is not at all uncommon in the latter half of the first year. There is a period of two or three days, often, when general sensitiveness, apparently referred to the lower extremities, may suggest rheumatism, but the presence of characteristic ulcerative stomatitis, the tenderness in the epiphysis, rather than the joint, and the rapid improvement following the administration of orange-juice, point to the scorbutic nature of the symptoms.

Acute Osteomyelitis.—In this condition the onset is likely to be ushered in with much higher temperature and more severe constitutional symptoms than are usual in rheumatic fever. The symptoms of inflammation about the focus of infection develop with great rapidity and are generally not articular. The leukocytosis is more pronounced, and the surrounding tissues are extensively involved.

Congenital Syphilis.—Syphilitic arthritis is a slow and not very painful affection. As the knee joints are especially liable to infection, confusion of diagnosis may exist for a time. A careful history, the search for other evidences of syphilitic manifestations, and the evidence of the Wassermann reaction make the distinction possible.

Tuberculous arthritis is far more difficult to differentiate clinically from subacute rheumatic arthritis. Evidence of tuberculosis elsewhere and the absence of the usual sequence of endocarditis and chorea may help in the diagnosis. A negative von Pirquet reaction may have some significance—a positive reaction can be looked upon only as confirmatory evidence.

In all cases of bone and joint infection simulating rheumatic fever, the greatest assistance is obtained from radiographs of the affected part. The evidence so obtained combined with the clinical symptoms makes a correct differentiation practically certain.

Still's Disease.—In this condition there is an insidious, progressive inflammation of the joints, mainly involving the peri-articular tissues, but with a small amount of effusion into the joints themselves. The arthritis is generally multiple, beginning in the knees and wrists and later extending to the fingers. The lymph-nodes in the region of the affected joints, and the liver and spleen, are considerably enlarged. Anemia, sweating, and pyrexia are prominent symptoms, but endo- and pericarditis are not so likely to occur. The relation of the disease to the rheumatic fever is still an open question, though it is not difficult to recognize the clinical type.

Arthritis deformans is rare in childhood, although the cases classed as Still's disease have been considered by some writers as belonging to this group. The very gradual onset, beginning with stiffness and going on to progressive, multiple joint involvement without bony involvement, together with the ineffectiveness of salicylates in the relief of symptoms, make the diagnosis quite clear except in the very earliest stages.

In all diseases in which acute arthritis is a pronounced symptom, the therapeutic action of the salicylates is considered of considerable diagnostic importance. An arthritis that is not promptly relieved by the salicylates must be looked upon as possibly not rheumatic in origin. Such an inference, however, cannot carry great weight in the presence of positive evidence, such as is contributed by the development of symptoms of endocarditis and chorea.

Gonorrheal rheumatism in children is seldom necessary to differentiate from acute rheumatic fever. When it does occur it does not differ from its manifestations in adults. Very rarely it may be met with in babies within the first six weeks, when the disease has been contracted at birth from the mother. It is then generally associated with opthalmia. An examination of the discharges generally points to the diagnosis.

Gout is so seldom a disease of childhood that it is hardly necessary to consider its differential diagnosis from rheumatic fever. A case occurring under 30 years of age is likely to be rheumatoid arthritis.

There are other conditions which need only be mentioned and borne in mind. Anterior poliomyelitis, appendicitis, hemophilic arthritis, sprains, and separation of epiphyses may in some of their symptoms resemble rheumatic fever, but they present no difficulties in diagnosis.

Prognosis.—The prognosis in acute rheumatic fever as far as life is concerned is good so long as the heart remains unaffected. When death does occur, it is almost invariably through some form of carditis.

Children rarely die in their first attack, except in fulminating infections, which are very rare. The susceptibility to re-infections, or recurrences of attacks of rheumatic fever, increases greatly the danger that a heart slightly disabled in the first attack will become still more crippled in the second and third, by which time its reserve power has become largely depleted. Much depends upon the treatment which the child receives in his first attack. It has been said that a careful physician keeps his cases of rheumatic fever in bed for six weeks. If this were the general practice, the mortality of rheumatic fever would be much less than it is. The prognosis is really that of the heart condition. If the home conditions can be made hygienic, if diseased conditions of the teeth, throat, and nose are corrected with the very earliest rheumatic manifestations, the prognosis of the disease is favorably influenced by reducing the danger of re-infection. Unfortunately, it is not always possible to detect the portal of entry, and again, once infected, focal areas may remain in inaccessible places and become active in spite of the best care and hygiene. The younger the patient the greater the danger of recurring attacks. A strong family history of rheumatism is another unfavorable factor in the prognosis. Many of the children subject to rheumatism are handicapped by poverty and the problem of suitable food, clothing and climate may be insuperable. Still, it is not well to be too pessimistic in such cases. If a child has been once treated for rheumatic fever, its parents should be fully informed of the serious nature of the disease and warned not to under-estimate the early symptoms. Prompt and energetic measures instituted early, even in recurring attacks, are often effective in limiting the infection. There is no class of cases in our hospitals which are so benefited by a careful follow-up system. There is no question but that many lives are saved in institutions where supervision of its patients is maintained after a first attack.

Treatment.—Preventive.—From what has been written of the etiology of the rheumatic fever, it would naturally follow that the most important measures to be taken in reference to prevention of infection would depend upon maintaining a normal condition of health in the portals of entry of the infectious agent. Whereas it is difficult to bring positive proof as to the part played by tonsillitis and dental caries in the etiology of the disease, common sense points to the wisdom of keeping the oral and nasal cavities in the best possible condition of health. This means that a large proportion of children in our hospital clinics and public schools should receive much more frequent dental inspection and care than is now carried out. Indiscriminate operations for the removal of tonsils and adenoids are not advised; but there is no question of greater importance for the pediatrist to decide than that of the advisability or non-advisability of operation. In doubtful cases in which symptoms of general debility persist in spite of regulation of diet, hygiene, and treatment with stomachics and iron, or malt and cod-liver oil, marked improvement generally follows adenectomy and tonsillectomy, assuming, of course, the existence of marked hypertrophy or ragged, irregular enlargement of moderate degree, with chronic adhesions between the tonsils and the anterior and posterior pillars of the fauces.

If suspicious early symptoms of rheumatism are present, or if there is a history of previous attacks, the indications for operation are very much strengthened. In the opinion of the writer, these measures are less effective in cases in which chorea predominates than in those especially characterized by tonsillitis and arthritis. The observation, if correctly made, may be explained by the possible fact that many choreas are not rheumatic, but due to other undetermined factors.

Exposure to cold, damp, bad ventilation and drainage are predisposing conditions which should be corrected when possible. It is rarely possible to order a change of climate, but among the well-to-do it may be a wise prescription, especially after a first attack in which the heart has suffered some damage. Winters and springs spent in a warm, dry climate may ward off the dangerous recurrent attacks and allow the heart muscle a longer time to recover its tone.

School physicians and teachers should be familiar with the early signs of chorea. Too many children are classed as "fidgety" and "nervous" who are choreic. Their removal from school when the symptoms are in these early stages will in the long run shorten the inevitable interruption of their attendance.

Management of the Acute Attack.—There are principles of treatment to be carried out irrespective of the severity of the attack, for from the mildest beginnings the most serious cardiac infections may occur.

Rest.—Most important of all, especially in children, is complete rest in bed, often for a period of from four to six weeks. Parents and patients frequently rebel at such a radical interruption of the child's daily routine, especially if in a few days the acute symptoms subside under salicylate treatment. Rest in bed accomplishes several purposes. It minimizes the waste of tissues occasioned by fever. The horizontal position, furthermore, reduces blood pressure and cardiac action and lessens the danger of cardiac complications, for it has been shown that the mechanical injury to the heart valves incident to overaction of the heart muscle is an important factor predisposing to rheumatic and other inflammatory infections of the valves. A third benefit is found in the favorable conditions induced by rest for the subsidence of inflammations of the joints.

The period of rest is determined by the subsidence of all acute symptoms, such as tonsillitis, arthritis, and fever. One of the earliest and most valuable indications of cardiac involvement is a marked increase in the pulse rate. When this persists in spite of the defervescense of the fever, it must be looked upon as a danger signal, and one will seldom err in judgment if the period of rest in bed is continued until the rate has become normal. Similarly the pulse rate is a valuable guide as to the rapidity with which one may push the convalescence. Beginning with an hour of sitting up in bed in the morning and again in the afternoon, the time is gradually increased until the child progresses to a chair, then to out-of-door rest, then to short walks and rides—and with great caution back to the routine activities of childhood. A careful observation during the convalescence should be kept of the pulse rate, for over-exertion invariably shows in a sharp and continued elevation of the curve. Slight irregularity and intermittency should always be judged in connection with the pulse rate; it is not uncommon in children to have a certain arrhythmia and even intermittency after acute illnesses, which may last for years. If the pulse rate keeps within normal limits, less significance may be attached to such variations, and one may avoid undue restrictions upon the child's activities.

The development of cardiac murmurs may mean only a relative insufficiency of the valves which is restored during the period of convalescence. If it persists it generally indicates valvular disease, and is likely to be permanent. Here, again, the pulse rate is the main point which guides us in determining the activities of the child. The medicinal treatment of cardiac disease of rheumatic origin will be found in the special chapter on carditis.

Local rest of the joints is further secured by bandaging over cotton wadding, or by splints in severe cases. The first effect is often unpleasant to the patient, but the ultimate benefit justifies a reasonable amount of initial discomfort, and results in more rapid improvement. The splints may be so arranged as to permit local applications, if these are considered desirable.

If there is profuse sweating, then flannel nightgowns or pajamas are preferable to cotton or linen. Warm alcohol sponges and drying with a soft towel and the use of talcum powders will alleviate this uncomfortable symptom. The room in which the patient is confined should be well ventilated and comfortably warm. Cold-air treatment, so useful in many conditions, has its distinct limitation in this disease.

Diet.—The origin of the idea of the harmfulness of acids, meat, and a liberal diet in rheumatism dates back to the time when the cause of the disease was attributed to excess acid production. While it is true that the growth of the diplococcus rheumaticus is characterized by the free production of formic acid, the source of the acid is due to bacterial activity rather than to diet. On general principles which underlie the treatment of all acute diseases, overfeeding is to be avoided and the solid food is restricted, but the dieting once prevalent is not a part of modern treatment. In the subacute and chronic stages of the disease and in convalescence liberal feeding, with a view to building up the general nutrition of the body, is essental—and often improvement does not occur until this has been done.

In the active stages of the disease, milk, starchy foods, such as rice, cereals, bread and butter, and eggs are our main reliance. As convalescence develops measures should be taken to increase the appetite by simple stomachics and to overcome the anemia and malnutrition by a more liberal diet in which reasonable amounts of nitrogenous foods in the form of meats, chicken, and fish are a part. Malt and cod-liver oil is a most useful addition to the diet and should be looked upon as food rather than as a medicine. Plenty of water should be given to maintain free renal action. Lemonade and orange-juice in moderation are permissible, and barley and oatmeal water and natural effervescent water or siphon soda are useful if not taken in such quantities as to interfere with the appetite for nourishing food.

Medicinal Treatment.—At the beginning of an attack with fever, a mild catharsis, by calomel or castor oil, is desirable. If there is obvious tonsillitis, chlorate of potash given internally, 10 to 20 gr. in the course of 24 hours, is a valuable adjunct to the salicylate treatment.

The use of salicylic acid in some form has been sanctioned by years of use. By some it is still heralded as a specific remedy. It is undoubtedly efficient in controlling pain and possibly in reducing fever and allaying inflammation of the joints. There is, however, no conclusive evidence that the salicylates shorten the course of the infection or lessen the liability to its worst manifestations, the occurrence of cardiac infections. It is not the practice of today to push the salicylate treatment to the extreme dosage that was once prevalent. It is good opinion that extensive use of this drug may even be detrimental to the patient. Rheumatic nodules and cardiac involvement frequently occur in spite of very large and long-continued use of the salicylates. They are, however, indispensable for the relief of pain, fever, and arthritis. When this has been accomplished they should gradually be discontinued. It is rarely desirable to extend their use beyond a fortnight.

Twenty to thirty grains of salicylate of soda, aspirin, novaspirin, salol or salicin, for a child of five years, is as efficient as larger doses and less liable to do harm. Salicylic acid itself is never used because of its irritating action on the stomach. Aspirin (acetyl-salicylic acid) is less disturbing to the stomach and bowels than salol or sodium salicylate. Novaspirin is a newer preparation similar to aspirin and said to be still less irritating, but if the dosage is kept down to reasonable limits one finds it difficult to verify some of the claims made on this point, for this and other similar preparations. Tolysin, another salicylate, has the advantage of being tasteless, and may therefore be used with advantage in the very young children who object to the taste of aspirin. Ringing in the ears, gastric disturbance, cardiac irregularity or weakness, or toxic manifestations with delirium represent in the order of severity unfavorable and depressing action of the salicylate and indicate the need of reduced dosage or total cessation of the asministration, irrespective of what amount has been used.

If moderate doses of salicylate do not relieve the symptoms of pain, it is better practice to supplement their use with some analgesic, such as antipyrine or acetanilid, alone or, still better, in combination with sodium bicarbonate and caffeine.

In extreme cases of pain codeine or morphine may be temporarily needed—either by mouth or in a suppository.

In protracted cases of rheumatic fever the medicinal measures should be along the line of general tonic treatment, iron, in the form of Blaud's pills, with or without arsenic, or some of the many newer and satisfactory preparations, and of a more liberal diet. As previously stated, malt and cod-liver oil is most valuable in this stage in children and may be continued for several months with benefit.

Alkaline Treatment.—The administration of alkalies in acute rheumatic fever dates back to the time when excess acid production was looked upon as the cause of the disease. They continue to be used, but with the idea of neutralizing the highly acid urine and controlling the excessive acid sweats which are frequently an unpleasant symptom. They serve as adjuvants to the salicylates rather than as substitutes for them. Bicarbonate of potassium and sodium are the most efficacious of the alkalies and are given up to the point of neutralization of the urine. They serve a further purpose when used in conjunction with sodium salicylate in neutralizing any free salicylic acid which may be liberated from its salts or compounds. There is reason to believe that larger doses of salicylates may be given if combined with the alkaline treatment. Tribasic citrocarbonate and Kalak water are pleasant and effective preparations of alkalies to use when bicarbonate of soda is distasteful.

Local Treatment.—The local treatment of arthritis is primarily rest in bed, and in extreme cases limitation of motion by splints or bandages. In addition, hot or cold applications, according to which is more acceptable to the patient. Ice bags are generally not borne well by children, when applied to an inflamed joint, though they may have a favorable action when placed, without too much weight, over the precordia in cases of pericarditis. Hot fomentations of lead water and laudanum, or the various ointments containing wintergreen, salicylates, camphor, menthol, or icthyol are soothing and anesthetic. These may be used in a 10 per cent. ointment and rubbed into the joint twice a day and cotton wadding with fixation applied. In subacute cases painting the joint with tincture of iodin or the use of some of the modern preparations of soluble iodin in an oily base are useful procedures.

Nervous Symptoms.—It is important to guard against exhaustion arising from pain, restlessness, or sleeplessness. Bromides, trional, or veronal will often secure rest and tide over the early days of discomfort. In cases of cerebral rheumatism with high fever ice bags to the head and cold packs must be freely used. Antipyretic drugs are apt to be dangerous in doses sufficient to be effective. More powerful sedatives, such as morphine or hyoscine by hypodermic injection, are often required. Temporary cardiac weakness is best treated by caffeine, sodium benzoate, or camphor in oil, subcutaneously.

Serum and Vaccins.—Serum and vaccin treatment have not proved consistently beneficial in acute rheumatic fever. It is not the intention to discount unfavorably possible advances along these lines in the future. The use of stock anti-streptococcus sera is, however, at present of doubtful expediency and there are insuperable difficulties at present in obtaining autogenous vaccins.

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CHAPTER CXLI

DIPHTHERIA

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The lesions and symptoms of diphtheria are caused by toxemia. The concentrated poison at the seat of the exudate causes local inflammation, while in the more severe cases the absorbed poison diffused throughout the body causes widespread cellular injury.

This specific contagious disease can be traced back under various names to almost the Homeric period of Grecian history. From time to time during the following centuries we hear of epidemics which indicate that the disease never ceased.

In 1771 Bard, an American, advanced strong reasons for believing that membranous croup and pharyngeal diphtheria were different manifestations of the same disease process. His views have been corroborated by bacterial findings.

In 1821 Bretonneau published his first essay on diphtheria in Paris and gave to the disease its present name.

The Diphtheria Bacillus.—As early as 1840 observers began to notice microörganisms in the pseudomembranes. Gradually the observations became more exact. The most importance at first was attributed to micrococci. These later were shown to be secondary invaders. In the year 1883, bacilli which were very peculiar and striking in appearance were shown by Klebs to be of constant occurrence in the psuedomembranes from the throats of those having characteristic diphtheria. He described the peculiar staining of the organisms. One year later Löffler separated these bacilli from the other bacteria and grew them in pure culture. They have therefore sometimes been called Klebs-Löffler bacilli. When the bacilli were inoculated upon the abraded mucous membrane of susceptible animals more or less characteristic pseudomembranes were produced, and frequently paralysis followed with characteristic lesions. These animal experiments have been fortified by a number of accidental human inoculations with pure cultures of bacilli with subsequent development of diphtheria.

This bacillus is one of the most interesting of bacteria and a knowledge of its most important characteristics are of extreme importance to physicians. Grown in the animal body or in suitable culture fluid, it produces a powerful toxin. As little as 0.0005 c.c. of the filtered culture fluid sometimes kills a guinea pig. Its morphology and staining are peculiar and these characteristics allow of it quick identification.

Outside of the body it grows best on serum media, and these media either coagulated or in fluid condition are used for diagnostic cultures.

Morphology.—When cover-glass preparations made from the exudate or from the cultures grown on blood serum, are examined, the diphtheria bacilli are found to possess the following morphological characteristics: The diameter of the bacilli varies from 0.3μ to 0.8μ and the length from 1μ to 6μ. They occur singly and in pairs (Fig. 1). The rods are straight or slightly curved, and usually are not uniformly cylindrical throughout their entire length, but are swollen at the end, or pointed at the ends and swollen in the middle portion. The two bacilli of a pair may lie with their long diameter in the same axis or at an obtuse or an acute angle. The bacilli possess no spores, but have in them highly refractive bodies, some of which are the starting point for new bacilli.

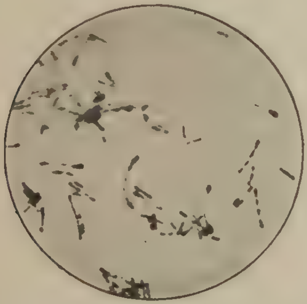

FIG. 1.—One of the very characteristic forms of diphtheria bacilli from blood-serum cultures, showing clubbed ends and irregular stain. × 1100 diameters. Stain, methylene blue. (Park and Williams.)

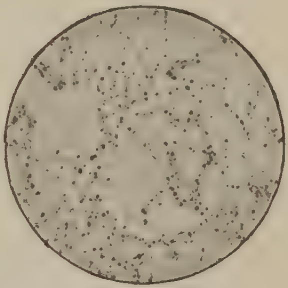

FIG. 2.—Virulent diphtheria bacilli, showing stain with Neisser's solutions. This appearance was formerly supposed to be characteristic of virulent bacilli, but non-virulent bacilli often stain in the identical manner. Bodies of bacilli in smear, yellowish brown; granules, dark blue. (Park and Williams.)

Staining.—Diphtheria bacilli stain readily with ordinary aniline dyes, and retain fairly well their color after staining by Gram's method. With Löffler's alkaline solution of methylene blue, and to a less extent with other stains such as Roux' and dilute Ziehl's solution, the bacilli from blood-serum cultures especially, and from other media less constantly, stain in an irregular and extremely characteristic way. The bacilli do not stain uniformly. In many cultures round or oval bodies, situated at the ends or in the central portions, stain much more intensely than the rest of the bacillus. The same round or oval bodies which take the methylene blue more intensely than the remainder of the bacillus are brought out still more distinctly by the Neisser stain (Fig. 2).

This stain has been advocated in order to separate the virulent from the non-virulent bacilli, without the delay of inoculating animals; but in our hands, with a very large experience, nothing but animal inoculation with the suspected bacilli together with control injections of diphtheria antitoxin will accurately separate harmless bacilli from those capable of producing diphtheria.

Growth in Ascitic or Serum Bouillon.—All varieties of diphtheria bacilli grow exceedingly well in this medium, even when first removed from the throat. They almost always form a slight pellicle at the end of 24 hours. This increases up to the end of 48 hours. This culture medium is, as pointed out by Williams, of the greatest value in obtaining pure cultures for virulence tests in doubtful clinical cases or persistant carriers, since attempts to get these directly from solidified serum cultures containing few diphtheria bacilli among many other bacteria are apt to fail. Plate cultures are made from the pellicle. The fluid is prepared by adding to the nutrient bouillon 25 per cent. ascitic fluid or blood serum. The virulence test requires about four days for its completion.

Growth in Milk.—The diphtheria bacillus grows readily in milk. It does not increase at temperatures below 15°C. At 20°C. it develops fairly rapidly. This development at temperatures fairly common in milk favors the dissimination of diphtheria by milk which has become slightly infected from a carrier and accounts for the occasional outbreaks caused by raw milk.

Diphtheria Toxin.—This poison was assumed by Löffler (1884) to be produced by the bacilli, but it was first partially isolated by Roux and Yersin, who obtained it from cultures of the living bacilli by filtration through porous porcelain. Its striking specific characteristic, is that when it is inoculated into suitable animals in non-fatal doses it produces antitoxin. It has not yet been successfully analyzed, so that its chemical composition is unknown, but it has many of the properties of protein substances. After injection into the body in lethal doses there is a latent period before its poisonous action appears. At the seat of inoculation there appears later a grayish focus surrounded by an area of congestion; the subcutaneous tissues for some distance around are edematous; the adjacent lymph-nodes are swollen, and the serous cavities, especially the pleura and the pericardium, frequently contain an excess of fluid usually clear, but at times turbid; the lungs are usually congested, the suprarenals are markedly congested. From the area surrounding the point of inoculation virulent bacilli may be obtained, but in the internal organs they are only occasionally found, unless enormous numbers of bacilli have been injected. Paralysis, commencing usually in the posterior extremities and then gradually extending to the whole body and causing death by paralysis of the heart or respiration, is also produced in many cases in which the inoculated animals do not succumb to a too rapid intoxication. In a number of animals we have seen recovery take place three to six weeks after the onset of the paralysis.

Virulence of Bacilli and Severity of Case.—From the severity of an isolated case the virulence of the bacilli cannot be determined. The presence of slight amounts of antitoxin in the blood of the person attacked and the association of other bacteria are at least two of the important disturbing factors. The most toxic bacillus we have ever found was obtained from a mild case of diphtheria simulating tonsillitis. Another case, however, infected by this bacillus proved to be very severe. In localized outbreaks the average severity of the cases probably indicates roughly the toxicity of the bacillus causing the infection, as here the individual susceptibility of the different persons infected would, in all likelihood, when taken together, be similar to that of other groups but even in this instance special conditions of climate, food, or race may influence certain localities. It must be remembered that bacilli of like toxic power may differ in their liability to infect the mucous membrane; that is, the virulence of the organism may not go hand in hand with the toxicity. Upon this point we have no certain knowledge.

Types of Diphtheria Bacilli.—There are distinct immunological differences among diphtheria bacilli. They resemble in this respect the pneumococci. Five main types have been noted. The antitoxin produced by anyone is effective against the toxin of every type. The bactericidal properties of the sera differ. Some believe that a serum should have polyvalent bactericidal properties along with its antitoxin content. There is no proof that a serum containing bactericidal and antitoxin properties is any better than one having antitoxic action alone.

Virulent Bacilli in Healthy Throats.—Fully toxic bacilli have frequently been found in healthy throats of persons who have been brought in direct contact with diphtheria patients or diphtheria carriers without contracting the disease. It is therefore apparent that infection in diphtheria, as in other infectious diseases, requires not only the presence of toxic bacilli, but also a susceptibility to the disease, which may be local or general. We know that 70 per cent. of persons in cities are protected from infection because of having antitoxin in their blood. Among the predisposing influences which contribute to the production of diphtheritic infection may be mentioned the breathing of foul air and living in overcrowded and ill-ventilated rooms, impure food, certain diseases, more particularly catarrhal inflammations of the mucous membranes, and depressing conditions generally. Under these conditions an infected mucous membrane may become susceptible to disease. In connection with Beebe (1894) we made an examination of the throats of 330 healthy persons who had not come in contact, so far as known, with diphtheria, and we found toxic bacilli in eight, only two of whom later developed the disease. In 1923 I watched 30 children who were found to be carriers and none of them developed diphtheria. In 24 of the 330 healthy throats non-toxic bacilli similar to the toxic diphtheria bacillus were found. Very similar observations have since been made in Boston and by others in many widely separated countries. In 1905 Von Sholly in our laboratory examined 1000 throats of those who had not knowingly been in contact with diphtheria and found toxic diphtheria bacilli in 0.5 per cent. of the cases. We have found toxic bacilli in about 5 per cent. of cases of scarlet fever. This indicates they are more prevalent in throats than a single culture from normal cases indicated.

Persistence of Diphtheria Bacilli in the Throat.—The continued presence of toxic diphtheria bacilli in the throats of patients who have recovered from the disease has been demonstrated by all investigators. In the investigations of 1894 we found that in 304 of 605 consecutive cases the bacilli disappeared within three days after the disappearance of the pseudomembrane; in 176 cases they persisted for seven days, in 64 cases for 12 days, in 36 cases for 15 days, in 12 cases for three weeks, in four cases for four weeks, and in two cases for nine weeks. Since then we have met with a case in which they persisted with full toxicity for eight months. Since then many observers have reported those tests with similar results. It is safe to say that in over 10 per cent. of the cases a few bacilli persist two weeks after the disappearance of the exudate and in over 1 per cent. four weeks. It is extremely difficult to prove that a case is absolutely clear, as the bacilli may remain hidden in the epithelial cells of some tonsillar crypt and not be detected by cultures.

Classification of Carriers.—Those harboring diphtheria bacilli after recovery from disease may be called convalescent carriers; those who carry the bacilli in their throats or adnexa though they have never given evidence of clinical diphtheria may be called contact carriers. As the bacilli pass from one contact carrier to another they gradually decrease in virulence even though they still produce toxin. These two groups may be transient carriers or chronic carriers. In chronic carriers the removal of hypertrophic lymphatic tissue aids the disappearance of the bacilli. Some crypt of the tonsils is usually the seat of the infection.

Diphtheria-like Bacilli Not Producing Diphtheria Toxin.—In the tests of the bacilli obtained from hundreds of cases of suspected diphtheria which have been carried out during the past 20 years in the laboratories of the Health Department of New York City, in over 95 per cent. of cases the bacilli derived from exudates or pseudomembranes and possessing the characteristics of the Löffler bacillus have been found to be toxic, that is, producers of diphtheria toxin. But there are, however, in inflamed throats as well as in healthy throats, either alone or associated with the toxic bacilli, occasionally bacilli which, though morphologically and in their behavior on culture media identical with the toxic diphtheria bacillus, are yet producers, at least in artificial culture media and the usual test animals, of no diphtheria toxin. These bacilli so far as are known are harmless saprophytes. Between bacilli which produce a great deal of toxin and those which produce none we find a few minor grades of toxicity. We believe, therefore, in accordance with Roux and Yersin these non-toxic, but otherwise diphtheria-like, bacilli should be considered as possible attentuated varieties of the diphtheria bacillus which have lost their power to produce diphtheria toxin. This supposition is, however, not proved and it may be that the ancestors of these bacilli were never toxin producers.

It is our belief therefore that the great majority of these bacilli have lost permanently, if they ever had it, their pathogenic properties.

Among the non-toxic diphtheria-like bacilli which are obtained frequently from normal or slightly inflamed throats or from other mucous membranes are some that may be slightly virulent for guinea pigs since they may kill, as we found, in dose of 2 to 5 c.c. of broth culture subcutaneously or intraperitoneally injected. The action of these bacilli is not due to diphtheria toxin. At autopsy the bacilli are usually found more or less abundantly in the blood and internal organs.

Resistance to Heat, Drying, and Chemicals.—The thermal death-point of B. diphtheræ with 10 minutes' exposure is about 60°C. with three minutes 70°C. Boiling kills almost instantly. The bacillus has about the average resistance of non-spore-bearing bacteria to disinfectants. In the dry state and exposed to diffuse light diphtheria bacilli usually die in from a few hours to a few days, but they may live for months; when in the dark, or protected by a film of mucus or albumin, they may live for even longer periods. Thus we found scrapings, from dry bit of membrane to contain vigorous and toxic living bacilli for a period of four months after removal from the throat, and if the membrane had not been at that time completely used, living bacilli could probably have been obtained for a much longer period. On slate and lead pencils, toys, tumblers, as well as on paper money, they may live for several weeks, while on metal coins they die in 12 to 36 hours. In culture media, when kept at the blood heat, they usually die after a few weeks; but under certain conditions, as when sealed in tubes and protected from heat and light, they retain their life and toxicity for years. The bacillus is not sensitive to cold, for we found about 10 per cent. of the bacilli to retain their vitality and toxicity after exposure for two hours to several hundred degrees below zero. At temperatures just below freezing they may remain alive and toxic for a number of weeks.

Transmission of Diphtheria.—The toxic bacilli have been found on soiled bedding or clothing of a diphtheria patient, or drinking-cups, candy, shoes, hair, slate pencils, etc. These sources of infection by which the disease may be indirectly transmitted are, however, the less important ones. The usual source of the bacilli are the discharges of diphtheria patients; the secretions from the nose and throat of convalescent cases of diphtheria in which the toxic bacilli persist, and from the healthy throats of individuals who acquired the bacilli from being in contact with others having virulent germs. When we consider the number of healthy carriers and that it is only the severe types of diphtheria that remain isolated during their actual illness, the wonder is not that so many, but that so few, persons contract the disease. The possibility of the transmission of diphtheria from animals to man cannot be disputed; we have met two instances in which cats had malignant diphtheria, and many other animals can be infected, but there are few if any authentic cases of such transmission on record. So-called diphtheritic disease in animals and birds is usually, if not always, due to other microörganisms than the diphtheria bacilli.

Susceptibility to and Immunity against Diphtheria.—An individual susceptibility, both general and local, to diphtheria, as in all infectious diseases, is necessary to contract the disease. Age has long been recognized to be an important factor in diphtheria. Children within the first six months of life are rarely susceptible, exceptionally infants of a few weeks are attacked. The time of greatest susceptibility is during the second and third years. After the third year susceptibility gradually decreases. Young animals born of mothers immune to diphtheria because of antitoxin possess nearly the same degree of immunity as their mothers. They gradually lose this but retain traces up to 6 to 12 months. The human infant is now known to receive immunity from its mother. This immunity has been shown to depend in part at least on the presence of antitoxin. Protective bactericidal substances may in some give moderate protection when antitoxin is absent.

The Persistence in Man's Blood of Homologous and Alien Antitoxin.—Antitoxins and other antibodies produced in an animal disappear more rapidly when introduced into the blood of another species than into one of the same species. In man an alien serum must be used in all except in the case of infants obtaining it from their mothers.

In our experiments in guinea pigs we have found that the homologous antitoxin was retained in appreciably amounts for at least six months, while the heterologous antibodies were noticeable to the same extent for only three weeks. There is a rather rapid loss of horse-produced antitoxin during the first few days and then a slow loss, becoming more and more gradual until final elimination at the end of ten days to three weeks. The larger the amount of antibodies injected the longer will be the time before the elimination has proceeded so far as to no longer confer immunity.

Relation of Bacteriology to Diagnosis.—We believe that all experienced clinicians will agree that there are certain mild exudative inflammations of the throat of similar appearance some of which transmit diphtheria while others do not.

The doubtful cases that have the diphtheria bacilli in the exudate, are capable of giving true characteristic diphtheria to others, or later develop it characteristically themselves, while those in whose throats no diphtheria bacilli exist can under no condition give characteristic diphtheria to others or develop it themselves. It is, indeed, true, as a rule, that cases presenting the appearance of ordinary follicular tonsillitis are not due to the diphtheria bacillus and do not harbor these bacilli. On the other hand, in small children mild cases very frequently occur with the semblance of rather severe ordinary follicular tonsillitis, which are found to be infected with the bacilli as well as the pyogenic cocci; and in large cities where diphtheria is prevalent all such cases must be isolated. Most observers agree with us in thinking that if in any case exposure to diphtheria is known to have occurred, even a slightly suspicious sore throat should be regarded as possibly infected with the diphtheria bacilli. If, on the other hand, no cases of diphtheria have been known to exist in the neighborhood, even cases of a more suspicious nature would probably not be regarded as infectious. Now that we know about 50 per cent. of children in the city and about 20 per cent. in the country have a fairly constant supply of antitoxin in their blood, we have reason to believe that many of these doubtful cases are simply diphtheria carriers in which the bacilli are taking little or no part in making the lesions. Like any carriers they are dangerous to others. Persons having tonsillitis due to streptococci is apt to be carriers of the diphtheria bacilli as frequently as normal persons.

The presence of irregular-shaped patches of adherent grayish or yellowish-gray pseudomembrane on some other portions than the tonsils is, as a rule, an indication of poisoning by the diphtheria bacilli.

Occasionally, in scarlatinal angina or in severe phlegmonous sore throats, patches of exudate may appear on the uvula or border of the faucial pillars, and still the case may not be due to the diphtheria bacilli; these are, however, exceptional. Thick, grayish pseudomembranes which cover large portions of the tonsils, soft palate, and nostrils are almost invariably the lesions produced by diphtheria bacilli.

The very great majority of cases of pseudomembranes of exudative laryngitis, in the coast cities at least, whether an exudate is present in the pharynx or not, are due to the diphtheria bacilli. Nearly all membranous affections of the nose are true diphtheria. When the membrane is limited to the nose the symptoms are, as a rule, very slight; but when the naso-pharynx is involved the symptoms are usually grave. Cases of catarrhal laryngitis in which there is no exudate are usually complications of a beginning influenza or other infectious disease.

Most cases of pseudomembranes and exudates, entirely confined to portions of the tonsils in adults, are not due to the diphtheria bacilli. Cases presenting the appearances found in scarlet fever, in which a thin grayish membrane lines the borders of the uvula and faucial pillars, are rarely diphtheritic. As a rule pseudomembranous inflammations complicating scarlet fever, syphilis and other infectious diseases are due to the activity of the pathogenic cocci and other bacteria, induced by the inflamed conditions of the mucous membranes due to the scarlatinal or other poison.

Paralysis following a pseudomembranous inflammation is an almost positive indication that the case was one of diphtheria, although slight paralysis has followed in very few cases in which careful cultures have revealed no diptheria bacilli. These, if not true diphtheria, must be considered very exceptional cases.

Bacteriological Diagnosis.—From the above it is apparent that fully developed characteristic cases of diphtheria are readily diagnosticated, but that many of the less marked, or at an early period undeveloped, cases are difficult or impossible to differentiate. In these cases cultures are of the utmost value, since they enable us to isolate those in which diphtheria like bacilli are found, and to give preventive injections of antitoxin to both the sick and those in contact with them, if this has not already been done. If there seems to be the slightest danger antitoxin should be given immediately as valuable time would, be lost in waiting for the cultures result. As a rule cultures do not give us as much information as to the gravity of the case as the clinical appearances, for before the lapse of the twelve hours required for the laboratory report, the extent of the disease usually allows a prognosis. The reported absence of bacilli in a culture must be given weight in proportion to the skill with which the culture was made, the suitableness of the media, the accessibility of the diseased parts and the knowledge of the one who examined it.

Diphtheria does not occur without the presence of the diphtheria bacilli; but there have been cases of diphtheria in which, for one or another reason, no bacilli were found in the cultures by the examiner. In many of these cases later cultures revealed them. The reverse is also true, the presence of diphtheria bacilli in throats without clear clinical signs of diphtheria in no sense makes it a case of diphtheria. A diphtheria carrier who possesses natural antitoxin cannot develop diphtheria but can as readily develop a streptococic tonsillitis as any one else. In a convalescent case the absence of bacilli in any one culture indicates that there are certainly not many bacilli left in the throat, but even repeated cultures cannot absolutely prove their total absence, for in some deep tonsillor crypt a few bacilli may remain in the epithelial cells. The physician must have intelligence to use advantageously laboratory findings.

Technique of the Bacteriological Diagnosis.—*Collection of the Animal Blood Serum and Its Preparation for Use on Cultures.*

Swab for Inoculating Culture Tubes.—The swab we prefer to use to inoculate the serum is made as follows: A stiff, thin, iron rod, 6 in. in length, is roughened at one end by a few blows of a hammer, and about this end a little absorbent cotton is firmly wound. Each swab is then placed in a separate glass tube, and the mouths of the tubes are plugged with cotton. The tubes and rods are then sterilized by dry heat at about 150°C. for one hour, and stored for future use. These iron rods have proved more serviceable for making inoculations than platinum-wire needles or wooden sticks, especially in young children and in laryngeal cases. It is easier to use the cotton swab in such cases and it gathers up so much more material for the inoculation that it has seemed more reliable. The wood unless very carefully selected is apt to break and is too thick to use in the nose.

For convenience and safety in transportation "culture outfits" have been devised, which consist usually of a small wooden box containing a tube of blood serum, a tube holding a swab and a record blank. These "culture outfits" may be carried or sent by messenger or express to any place desired.

Directions for Inoculating Culture Tubes with the Exudate.—The patient is placed in a good light, and, if a child, properly held. The swab is removed from its tube, and, while the tongue is depressed with a spoon, is passed into the pharynx (if possible, without touching the tongue or other parts of the mouth), and is rubbed gently but firmly against any visible membrane on the tonsils or in the pharynx, and then, without being laid down, the swab is immediately inserted in the blood-serum tube, and the portion which has previously been in contact with the exudate is rubbed a number of times back and forth over the whole surface of the serum. This should be done thoroughly, but it is to be gently done, so as not to break the surface of the serum. The swab should then be placed in its tube, and both tubes, thin cotton plugs having been inserted, are reserved for examination or sent to the laboratory or collecting station (as in New York City). If sent to Health Department laboratories for examination the blank forms of report which usually accompany each "outfit" should be filled out and forwarded with the tubes.

Where there is no visible membrane (it may be present in the nose or larynx) one swab should be rubbed over the mucous membrane of the pharynx and tonsils, and another in the nasal cavities, and a culture made from these. In very young children it should be remembered that the throat often contains food or vomited matter. This should be cleared away befored using the swab to make the bacteriological examination easier. Under no conditions should any attempt be made to collect the material shortly after the application of strong disinfectants (especially solutions of corrosive sublimate) to the throat. Cultures from the nostrils are often more successful if the nostrils are first cleansed with a spray of sterile normal salt solution.

Examination of Cultures.—The culture tubes which have been inoculated, as described above, are kept in an incubator at 37°C. for at least 12 hours, and are then ready for examination. When great haste is required, even five hours will often suffice for a sufficient growth of bacteria for a skilled examiner to decide as to the presence or absence of the bacilli. The absence of bacilli at this period cannot be relied upon. In primary cultures it is wise to reincubate tubes taken out under 16 hours in which no bacilli were found. A small percentage of these will yield positive results after a few hours' further incubation. On inspection it will be seen that the surface of the blood serum is dotted with numerous colonies, which are just visible. No diagnosis can be made from simple inspection; if, however, the serum is found to be liquefied or shows other evidences of contamination the examination will probably be unsatisfactory. If the physician uses care in selecting proper tubes he will have done much to obtain reliable information.

In order to make a microscopic preparation, a clean platinum needle is inserted into the tube and quite a large number of colonies are swept with it from the surface of the culture medium, a part being selected where the most suitable colonies are found. A sufficient amount of the bacteria adherent to the needle is washed off in a tiny droplet of water previously placed on the glass slide and smeared over its surface. The bacteria on the glass are then allowed to dry in the air. The glass slide is then passed quickly through the flame of a bunsen burner or alcohol lamp, three times in the usual way, covered with a few drops of Löffler's solution of alkaline methylene blue, and left without heating for 5 to 10 minutes. It is then rinsed off in clear water, dried, and mounted in balsam. When other methods of staining are desired they are carried out in the proper way.

In the great majority of cases one of two pictures will be seen with the $1/12$ oil-immersion lens—either an enormous number of diphtheria-like bacilli, with a moderate number of cocci, or an almost pure culture of cocci, mostly in pairs or short chains. In a few cases there will be an approximately even mixture of bacilli and of cocci, and in others a great excess of cocci. Besides these there will be occasionally met preparations in which, with the cocci, there are mingled bacilli more or less resembling the Löffler bacilli. These bacilli, which are usually of the pseudodiphtheria type of bacilli are especially frequent in cultures from the nose.

In not more than one case in twenty will there be any serious difficulty in deciding whether diphtheria-like bacilli are present or absent, if the serum in the tube is moist and has been properly inoculated. In the doubtful case another culture must be made or the bacilli plated out and tested in pure culture. The question of virulence can only be determined by animal tests. As these require four days to be carried out they are rarely made. The bacilli are treated as if they were virulent.

Direct Microscopic Examination of the Exudate.—An immediate decision without the use of cultures is often possible from a microscopic examination of the exudate. This is made by smearing a slide or cover-glass with a little of the exudate from the swab, drying, heating, staining and examining it microscopically. This examination, however, is much more difficult, and the results are more uncertain than when the slides are prepared from cultures. The bacilli from the membrane are usually less typical in appearance than those found in cultures and they are mixed with fibrin, pus and epithelial cells. They may also be very few in number in the parts reached by the swab, or bacilli may be found which closely resemble the Löffler bacilli in appearance, but which differ greatly in growth and in other characteristics and have absolutely no connection with them. When in a smear containing mostly cocci a few of these doubtful bacilli are present, it is impossible either to exclude or to make the probable diagnosis of diphtheria. Although in some cases this immediate examination may be of the greatest value, it is not a method suitable for general use, and should always be controlled by cultures. When carried out in the best manner an experienced bacteriologist may obtain markedly accurate results. Higley, in a series of consecutive throat cases, made the same diagnosis from the direct examination of smears as the Health Department laboratory made from the culture. To get the exudate he used a probe armed with a loop of heavy copper wire which had been so flattened as to act as a blunt curette. He then made thin smears from the exudate. After drying and fixing by heat the smears were stained for five seconds in a solution made by adding five drops of Kühne's carbolic methylene blue to 7 c.c. of tap-water. After washing and drying they were stained for one minute in a solution of 10 drops of carbol-fuchsin in 7 c.c. of water. The dilute solution should be freshly prepared. The diphtheria bacilli will appear as dark red or violet rods, and their contour, mode of division and arrangement are manifest.

Animal Inoculation as a Test of Toxicity.—It is important that physicians realize what a virulence test is and the time it takes to carry it out. Health Department laboratories should only be asked to make these time consuming tests when the bacilli persist for periods of over three weeks.

The So-called Virulence Test.—It must be remembered that the above described method if positive, only demonstrates the presence of bacilli having the morphology of diphtheria bacilli. Where a typical membranous inflammation exists, actual tests, as we have said, have shown that the bacilli are almost always true diphtheria bacilli, therefore for practical purposes they should be considered such and for quarantine purposes the cultures repeated until, as will occur in the majority, bacilli disappear. If positive cultures continue, or if it is a question of a normal carrier, a complete identification should be carried out, to release from quarantine those who may be harboring only harmless diphtheria-like bacilli. This determination is spoken of as the "virulence test," or the test for specific toxin production, as the final identification of a suspected diphtheria bacillus rests on the demonstration that it produces a toxin which is neutralized by known diphtheria antitoxin. This requires from three to five days.

Technic of Virulence Test.—The bacilli may be obtained in pure culture or the mixed bacteria of the original culture may be used. By the first method the first step in the test is the isolation of a pure culture of the bacillus. A number of plates are poured using nutrient agar or ascitic infusion agar (one part of ascitic fluid to five of agar). After hardening, the surface is streaked across with the growth from the Löffler serum tube, selecting when possible colonies which, in color and size, resemble those of the diphtheria bacillus and also using a general mixture preferably from the drier portions of the serum medium. After incubation for 16 hours at 37°C., the growth developing along the line of streak should be examined with the microscopic using a low power objective preferably a No. 2. Diphtheria colonies are most likely to be found at the edges of the streak. These are fished in the usual way by inserting a straight wire between the objective and the agar, the path of the wire and the actual touching of the correct colony being observed with the microscope. Care must be taken that the wire does not touch anything but the colony. The growth is transferred to ascitic fusion broth or Löffler medium depending on the subsequent method of test selected.

If very few bacilli are present in the original culture inoculations should be made into several tubes of ascitic broth. As the diphtheria bacillus will grow mostly on the surface of the broth, this portion can be used to inoculate plates with success where direct plates fail.

After determining that the cultures are pure and morphologically typical, animal inoculation is resorted to. When there are many diphtheria-like bacilli a moderate suspension of the mixed bacteria of the original diagnostic culture can be used. Two methods are available for the tests, the subcutaneous and the intracutaneous.

The Subcutaneous Method.—In this method, 1 c.c. of the ascitic broth culture (incubated 48 hours) or of a suspension of the mixed culture is injected subcutaneously into a guinea pig, about 250 gm. in weight. A second guinea pig is injected with same amount of culture to which had been added 50 to 100 units of diphtheria antitoxin. If the first pig dies within two to three days and on post-mortem, shows the typical engorgement of the suprarenals, and local edema already described and the second pig lives, the bacillus is a true toxin producing diphtheria bacillus, otherwise it is not.

The Intracutaneous Method.—The intracutaneous method requires some experience in recognizing the skin lesions. Its advantage is that four to six cultures can be tested with only two pigs.* The growth from a Löffler slant is rubbed up in 20 c.c. of salt solution and 0.15 c.c. injected intracutaneously into both pigs. The culture used must not be over 24 hours old. If the bacillus is a true diphtheria bacillus, it will develop toxin which will produce in the non-immunized pig a definite local inflammatory lesion after 24 hours which goes on to superficial necrosis in 48 to 72 hours. The pig receiving antitoxin will show no lesion. When the diagnostic culture is used and no diphtheria bacilli are present the other bacteria may excite an imflammatory reaction but so far as I know necrosis never develops.

Mixed Infection in Diphtheria.—Toxic diphtheria bacilli are not the only pathogenic bacteria present in human diphtheria. Various cocci and bacilli more particularly streptococci, staphylococci, pneumococci and influenza bacilli, are always found actively associated with Löffler's bacillus in diphtheria, playing an important part in the disease and leading often to serious complications (sepsis and bronchopneumonia). Investigations indicate that when other pathogenic bacteria are associated with diphtheria bacilli they mutually assist one another in their attacks upon the mucous membrane, the streptococcus being particularly active in this respect, often opening the way for the invasion of the Löffler bacillus into the deeper tissues or supplying needed conditions for the development of its toxin. In most fatal cases of bronchopneumonia following laryngeal diphtheria we find not only abundant pneumococci or streptococci in the inflamed lung areas, but also in the blood and tissues of the organs. As these septic infections due to the pyogenic cocci are in no way influenced by the diphtheria anitoxin, they frequently are the cause of the fatal termination. Other bacteria cause putrefactive changes in the exudate, producing alterations in color, *e.g.*, B. pyocyaneus and offensive odors, *e.g.*, B. fusiformis.

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* Rabbits may also be used.

Pseudomembranous Exudative Inflammations Due to Bacteria Other than the Diphtheria Bacilli.—The diphtheria bacillus, though the most usual, is not the only microörganism that is capable of producing pseudomembranous inflammations. There are numerous bacteria present almost constantly in the throat secretions, which, under certain conditions, can cause local lesions very similar to those in the less marked cases of true diphtheria. The streptococcus and pneumococcus are the two forms most frequently found in these cases, but there are also others, such as Vincent's bacillus, which, under suitable conditions, excite this form of inflammation, but without serious constitutional symptoms.

The pseudomembranous angina accompanying scarlet fever, and to a less extent other diseases, may not show the presence of diphtheria bacilli, but only the pyogenic cocci, especially streptococci, or, more rarely, some varieties of little-known bacilli. The deposit covering the inflamed tissues in these non-specific cases is, it is true, usually but not always, rather an exudate than a true pseudomembrane. The fact that exudates occur in cases which are absolutely known to have negative Schick tests is additional proof that diphtheria toxin is not required to produce these changes.

Diphtheroids.—There are a large number of small more or less irregular bacilli bearing some morphological resemblance to the diphtheria bacillus which have been loosely termed diphtheroids. They have been found in the nose, throat, eye and other parts of the body, both in health and in disease (Hodgkin's disease, leukemia, etc.). Several of them, *e.g.*, *B. hofmanni*, *B. xerosis*, are considered distinct species. Since this type of organism is so widely distributed, any specific pathogenic properties attributed to them, unless positive proof is offered, must be received with reserve.

There interest is chiefly because they may be taken for diphtheria bacilli.

Bacillus Hofmanni (Pseudodiphtheria Bacilli).—These bacilli are rather short, plump, and more uniform in size and shape than the true Löffler bacillus (Fig. 3). On blood serum their colony growth is very similar to that of the diphtheria bacilli. The great majority of them in any young culture show no polar granules when stained by the Neisser method and evenly throughout with the alkaline methylene blue solution. They do not produce acid by the fermentation of glucose, as do all known virulent and many non-virulent diphtheria bacilli; therefore there is no increase in acidity in the bouillon in which they are grown during the first 24 hours from the fermentation of the meat sugar regularly present. They are found in varying abundance in different localities in New York City, in about 1 per cent. of the normal throat and nasal secretions, and seem to have now at least no connection with diphtheria. They have been called *pseudodiphtheria* *bacilli*, and more properly *B. hofmanni.* In bouillon they grow, as a rule, less luxuriantly than the diphtheria bacilli. Some of the varieties of the pseudodiphtheria bacilli are as long as the shorter forms of the virulent bacilli. When these are found in cultures from cases of suspected diphtheria they may lead to an incorrect diagnosis. These bacilli are found occasionally in all countries where search has been made for them. There are also some varieties of diphtheroids which resemble the short *B. hofmanni* in form and staining, but which produce acid in glucose bouillon.

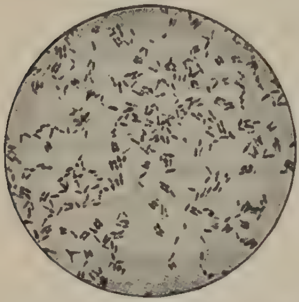

FIG. 3.—Pseudodiphtheria bacilli. (*B. hofmanni.*) (Park and Williams.)

Bacillus Xerosis.—Diphtheria-like bacilli were found by Kutschert and Neisser (1884) in the condition known as xerosis conjunctivæ. Since then they have been found frequently in normal conjunctivæ. These bacilli went by the name of xerosis bacilli. Under this name, no doubt, different observers have placed several varieties of bacilli morphologically, somewhat similar to the diphtheria bacilli. Knapp first limited the name to bacilli that ferment saccharose and not dextrin, in contradistinction to diphtheria bacilli which ferment dextrin and not saccharose. The fermentation tests for three of the diphtheria group, according to Knapp, may be shown as follows:

SPECIES	DEXTROSE	LEVULOSE	GALACTOSE	MALTOSE	SACCHAROSE	DEXTRIN
B. diphtheria......	+	+	+	+	−	+
B. xerosis.........	+	+	+	+	+	−
B. hofmanni.......	−	−	−	−	−	−

NOTE.—One per cent. sugar in Hiss serum-water media.

These reactions do not separate the diphtheria bacilli from a large number of the non-virulent bacilli morphologically like the diphtheria bacilli mentioned before.

Pathology.—The lesions that are characteristic of diphtheria are caused chiefly by the direct irritant action of the soluble toxin produced by the bacilli. The endotoxin of the substance of the bacilli is also poisonous but less so. It probably produces some constitutional symptoms but does not produce paralysis.

The local irritant action is characterized by pseudomembranous inflammation. The effect of the absorbed toxin is shown by degenerative changes in many cells throughout the body and these lesions are especially important in the heart, nerves and kidneys.

Complicating secondary infections of the lungs and elsewhere are usually incited by accompaning streptococci and other pathogenic bacteria.

The Local Effects.—The most characteristic lesions of diphtheria are those which occur in the mucous membranes of the pharynx, nasopharynx and larynx. The first noticeable change is the appearance of tiny grayish-white patches which are hardly elevated from the surface.

These patches are part of the epithelial lining and cannot be removed without leaving superficial bleeding erosions. These patches usually thicken and coalesque with more or less thick pseudomembranes. The changes are often confined to the tonsils or larynx and sometimes to other portions. In severe cases the pseudomembrane frequently covers the tonsils, uvula soft palate and pharynx or larynx. In the lighter cases the pseudomembrane is grayish in color and gives forth little or no odor, but in some of the more severe cases because of local hemorrhages and the activity of accompaning bacteria the pseudomembrane is discolored and foul smelling.

Swelling of the lymph glands under the jaw is present in severe cases and the degree to which this takes place indicates in some measure the severity of the toxemia.

The toxin causes degeneration and necrosis of the cells with which it comes in contact and the mucous membrane lying under the exudate is found to have lost more or less completely its epithelial layer. The walls of the capillaries and smaller arteries undergo hyaline degeneration. The infiltration from them causes much of the swelling.

The pseudomembrane is made up of necrotic epithelium with the coagulated exudate from the engorged blood-vessels and bacteria. In the earlier stages this false membrane is so closely united to the underlying mucous membrane that it cannot be separated without tearing it off and having a bleeding surface.

Later the accumulation of leukocytes between the deeper tissues and the exudate leads to a digestion of the fibrin net work and the loosening of the pseudomembrane.

The Distant Effects.—The extent of these depends on the amount of toxin absorbed and the presence or absence of traces of diphtheria antitoxin. It is now well established that in spite of traces of antitoxin in the blood persons may develop diphtheria. These cases do not absorb enough toxin to neutralize the antitoxin and so do not develop any general lesions from the diphtheretic infection with the possibly exception of the effect of toxin passing up the adjacent nerve fibers. In those cases in which no antitoxin is present there will be more or less pronounced general systemic poisoning. The lesions are degenerated in character and need not be described in detail except in the heart, kidney and nervous system. When living complications occur they are usually of the nature of bronchopneumonia and have the same pathology as when caused primarily by the streptococci, pneumococci, influenza bacilli or other bacteria.

Heart.—Fatty degeneration of the myocardium is frequently found. It may be slight and localized in foci or may be extensive and generalized. It may be so extreme that the muscle fibers are completely degenerated. Acute interstitial lesions also occur. The peripheral nerve fibers also show degenerative changes and the vagus itself may be involved. One or all of these changes may account for the impairment of the heart's action. Sudden death is believed to be due chiefly to the disintegration of the vagus.

Kidneys.—The lesions found in diphtheria are similar to those developing in other forms of infections. The changes vary from simple degeneration in the milder cases to the more serious forms of acute nephritis in the severe cases. The institial and glomerular changes are more common in the cases of fairly long duration.

Lesions of the Nervous System.—The results of investigations have established the existence of an ascending lymph stream in the perineural sheath or nerves. Walsh sums up our knowledge as follows, "toxins reach the central nervous system in part at least by this path and disseminate in the lymph spaces of the pia-arachnoid and in those in the substance of the cord. Here they give rise to an inflammatory reaction in the connective tissue elements of the cord, to chromatolysis in the nerve cells and to myelin degeneration in the spinal roots. These changes occur in those segments of the central nervous system bearing anatomical relationship to the nerve supply of the infective focus. The nerves from this focus show an ascending perineutritis spreading to the cord by the spinal ganglia and spinal roots. It is noteworthy in view of negative findings in the nerves in some cases of diphtheritic paralysis that the myelin degeneration occurs almost exclusively in the intramedullary course of the nerves, i.e., from the point where the neurilemma sheath is lost. Hence, it has been assumed that, either the presence of the neurilemma sheath, or, more probably, the peripheral situation of the lymph channels protects the myelin sheaths in the peripheral course of the nerves."

In severe cases the toxin not only passes up the perineural lymph stream, but also by the general lymphatics of the region to the blood stream. From the capillaries the toxin passes to the tissues of the body and so leads to widespread degenerative changes in the substance of the cord and brain, and in the nerve fibers.

There seems then to be a twofold mechanism in the production of diphtheritic paralysis in man. There is the initial sometime severe and relatively short lived "local" paralysis, due to the action of the toxin, which has ascended in the nerves innervating the local lesion, on the nerve nuclei in the brain stem. Secondly there is the later, longer lasting, "generalized" paralysis, which is part of the general systemic toxemia.

Diphtheria may be classified according to location into pharyngeal, laryngeal, nasal, ocular, cutaneous, etc., or according to severity into mild, severe and septic.

Under six month of age diphtheria is not common due to the fact that these very young cases retain a passive immunity derived from their mothers. Nearly one-half of the cases admitted to the diphtheria wards of the Willard Parker Hospital occur during the period of from one to five years of age. From then on the age incidence diminishes fairly rapidly. Adults do not so frequently contract the disease. Laryngeal and nasal forms of diphtheria are almost invariably confined to children. In the septic forms there may be however, an extension to the larynx or to the nose in adults. Ocular diphtheria occurs generally in children.

A slightly larger number of females have been admitted during the past five years than males.

It is more prevalent during the cold months of the year than during the summer.

The infection is most commonly transmitted directly from one person to another. It is estimated that there are 50,000 people in New York City harboring virulent bacilli in their throats and these carriers may not present any clinical manifestations in themselves but may produce virulent infections in susceptibles with whom they come in contact. Cases may be so mild that they pass unnoticed and yet be a means of spreading the disease. The larger percentage of immunes in the cities is very striking. One of the writers (Park) has estimated by means of the Shick test the following age table of susceptibility:

	Per Cent., Country	Per Cent., City
Under 3 months	30	15
3 to 6 months	50	30
6 months to 1 year	80	60
1 to 2 years	85	70
2 to 3 years	75	55
3 to 5 years	70	40
5 to 10 years	65	30
10 to 20 years	60	20
Over 20 years	50	15

Recurrent attacks occur. One of the resident staff contracted diphtheria twice within a period of four months.

Occasionally all the members of a family come down with the disease and generally in a severe form. In the last six months two families were admitted in which all the children died.

The incubation period varies from about one to five days.

Symptoms.—The onset of the disease may be insidious or sudden. There are general signs of infection present, such as headache, drowsiness, malaise etc. Headache is a symptom very generally complained of. Nausea and vomiting are not very usual though occurring occasionally. The temperature is slightly elevated 99 to 100°F. One of the resident staff gave the following description when she contracted a mild form of diphtheria. On the first day there was some headache, malaise and a feeling of drowsiness with some slight temperature. On the second day the temperature was 99 to 100°F. the headache persisted and for the first time the throat was felt to be sore and showed small white patches scattered on each tonsil. The throat gave more a sensation of fullness than actual pain. The appetite was unimpaired when the throat became sore but the disinclination to eat was not due to any difficulty or pain on deglutition. The glands at the angle of the jaw were palpable and tender. On the third day the headache was still present, the throat felt about the same with some dryness and the scattered patches had coalesced into a grayish-white membrane about the size of a dime on each tonsil.

It is apparent that the local and constitutional symptoms may be so mild that the patient may continue at work. The throat symptoms may pass unnoticed or be taken to be what is commonly known "as catching cold." In young children, the indisposition may be so slight as to escape the notice of unobservant parents.

In severer forms the onset is usually more sudden, the headache is more severe and the prostration more extreme. The patient looks more acutely ill. Frequently the face is flushed and the breath has an offensive odor. The cervical glands show more enlargement and the throat a greater amount of membrane on the tonsils extending to the pillars and uvula and there is more swelling of the tissues. The temperature does not usually go above 100 to 101°F. There is not as a rule any delirium—the patient being more dull and apathetic and desiring to be left undisturbed. Restlessness is not usual. The throat symptoms are those of intense fullness, dryness and uncomfortableness rather than severe pain, and deglutition is not nearly so painful as later when the membrane has cleared. There may be some salivation but it is not as a rule pronounced.

In septic forms the prostration is extreme, the face has a pronounced pallor and waxy appearance. There may be delirium out of which the patient can however be aroused. Swallowing is difficult. The glands of the neck are greatly swollen. The swelling is white, shiny and glistening, and presents a mass uniform on account of edema of the tissues between the glands. An exudate covers the tonsils, uvula, soft palate, and sometimes extends into the nasal and post-nasal space causing mouth breathing, or down into the larynx impeding respiration. Hemorrhages may occur into the skin in the form of purpuric spots or from the mucous membrane of the mouth, nose, rectum etc. The temperature may go to 104°F. Salivation is frequent and irritating to the skin and mucous membrane at the corners of the mouth. There is often an excoriating serosanguinous nasal discharge.

The onset in the laryngeal form is usually gradual. The voice becomes husky and there is a brassy cough. Some dyspnea is present. The child has some fever and is inclined to be a trifle restless and irritable. There is generally an exudate on the tonsils, but in a fair percentage of cases the involvement is primarily in the larynx. In more severe cases the membrane may extend downward to the trachea and bronchioles, and in such cases whole casts of the tracheobronchial tree may be coughed up; the voice becomes less distinct and the dyspnea inspiratory. Occasionally expiratory dyspnoea is observed when the diphtheritic membrane is implanted low in the respiratory tract. Retraction of the sternum, supra- and infraclavicular spaces become pronounced. The child has to sit up to breathe, clutches at its throat and seizes the edges of the crib to bring into play the accessory muscles of respiration. Cyanosis and sweating supervene and exhaustion rapidly occurs.

Nasal diphtheria by itself is not very common but is seen more frequently as an extension from the severe and septic forms. There are forms of rhinitis in which plugs of membrane may be seen or in which there is purulent non-irritating discharge but generally an absence of constitutional disturbance. A plus culture of diphtheria may be found in a number of these cases but none of the complications or sequelæ of diphtheria as a rule follow. Other cases show a watery bloody discharge excoriating lip and nostrils with enlarged glands and signs of systemic poisoning.

Ocular diphtheria is not so common as one might at first suppose. It is characterized by swelling and infiltration of the eyelid and a watery bloody discharge. It may vary from mild to severe. The eyelid in typical cases is intensely swollen and red and on eversion shows a grayish-white membrane. There is an infiltration of the lid in addition to the edema. In severe cases corneal involvement with ulceration and perforation occur and the eye is lost. Sometimes both eyes are involved. In mild cases there is recovery without loss of vision. With ocular diphtheria there is generally tonsillar diphtheria and in severe cases with loss of eye the patients admitted to Willard Parker Hospital have succumbed to the virulence of the infection.

One of the writers (Dickson) has seen only two cases of skin diphtheria, one as the result of being bitten on the finger when the mouth gag slipped during intubation and the other in a wound on the cheek which would not heal until antitoxin was given. Both cases showed membrane and exhibited constitutional disturbance.

The amount of fever in diphtheria is usually not of much importance at the beginning of the illness. Sometimes in mild or in severe cases it may go to 104°F. and in septic forms it is usually quite high. In the mild forms it reaches normal in two or three days and in severe and septic forms it takes two or three days longer. Temperature persisting after this time usually means the occurrence of some complication. The administration of antitoxin causes a fall in temperature (Figs. 4, 5). The laryngeal type of the disease may exhibit a temperature curve gradually normal in from five to seven days unless a complication like pneumonia intervenes. In severe and septic cases the temperature may remain subnormal when it drops.

In mild cases there is not a great increase in the pulse rate but it is usually greater than would be expected from the amount of temperature. In severe and septic cases the pulse is weak and irregular and easily compressible. The muscular tone to the heart sounds is lost and murmurs are heard in nearly all cases, systolic in character, present one day and gone the next. Arrhythmia, gallop, rhythm, tachycardia and murmurs with alteration in the sounds at the apex may, one or all, occur in the course of severe and septic forms. The pulse at the wrist may become imperceptible. There is sometimes a very rapid drop in pulse rate which is of grave prognostic omen.

The exudate begins usually as small white patches which may coalesce very rapidly or may not coalesce at all. At first the membrane is thin, filmy, grayish-white in color and in a short time—a few hours to 24 hours—it becomes thicker. It may appear on one or both tonsils and in mild cases does not usually go beyond the size of a dime or a nickel. It is tough, tenacious and separates from the mucous membrane reluctantly leaving a bleeding surface. After reaching its maximum growth—two to three days its color becomes dark gray or black from extravasated blood and then it begins to curl up at the edges and exfoliates sometimes in one piece but generally it takes two or three days to disappear. Usually the raw service is covered with a thin filmy secondary membrane under which healing occurs. In more severe forms the membrane is greater in extent, covers uvula, pillars, soft palate and extends upward or downward. It has a tendency to "heap up" on the uvula and also on the epiglottis and arytenoids in the laryngeal type. In the septic forms the exudate is apparently not so well organized and it disintegrates in small particles more frequently. Sometimes the septic forms however have a considerable thickening of membrane all over the soft palate which may loosen in one piece and be expectorated. When decomposition of the exeudate occurs the breath is very offensive but it is not different

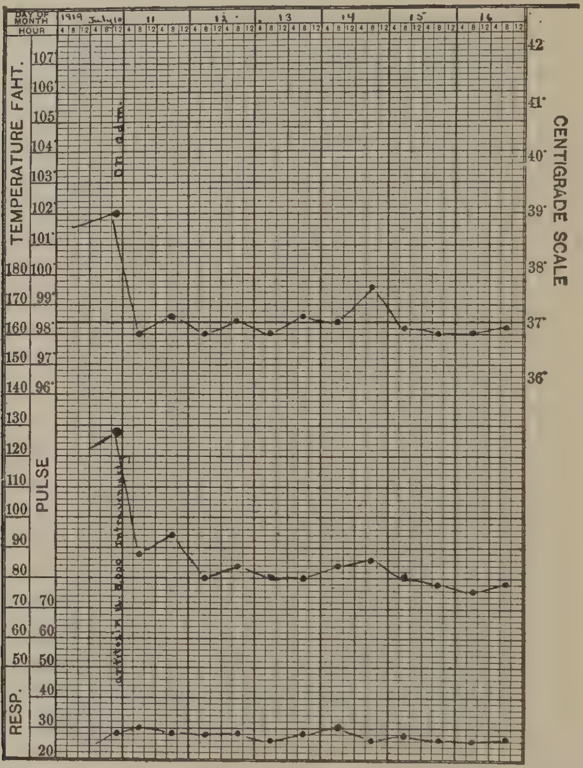

FIG. 4.—A type of chart frequently seen in uncomplicated cases of diphtheria after intravenous injection of antitoxin. Note the rapid fall of temperature and pulse rate to normal.

from the odor of necrosis elsewhere nor diagnostic of diphtheria. It should always however, suggest its possibility.

A mild case of diphtheria runs a course of about six days for its onset, the formation of membrane and its exfoliation. The mucous membrane quickly heals and it is difficult to restrain most of the patients or keep them in bed. It may be said that the mildest cases will show some quickening of the heart's action, but no complications or sequelæ as a rule follow. In the hospital they are kept in bed 10 days and on the twelfth day they are cultured for discharge. When two consecutive negative cultures on two successive days are obtained the patients are sent home.

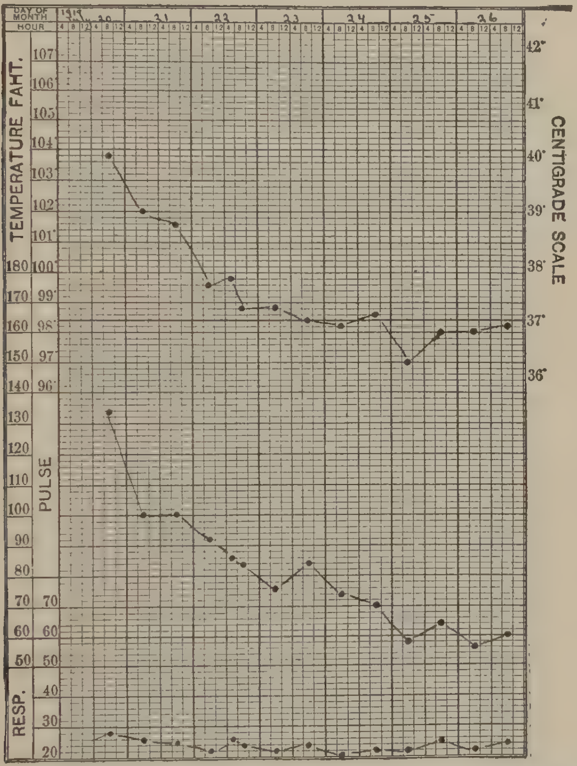

Fig. 5.—A septic case of diphtheria ill six days. Received 9000 units of antitoxin intravenously. The fall in temperature is more gradual than in Fig. 4. Note the bradycardia. This patient recovered.

In the more severe forms of the disease the local and constitutional symptoms are greater. The exudate is more extensive and takes longer to exfoliate. The glandular involvement subsides in from four to six days. Very rarely is there suppurative adenitis. Towards the end of the second week complications make their appearance the most frequent being paralysis of the palate. Subsequently other paralyses may follow and in favorable cases the duration extends into from four to six weeks longer. Occasionally the toxemia is so severe that death occurs in from two to three days.

In the septic forms the majority of the patients succumb to systemic poisoning in from five to seven days. If they pass through this period the intense swelling and edema of the throat and of the cervical and submaxillary glands subside but there is extreme danger from later paralyses and involvement of some vital structure. As late as the fifth or sixth week some paralysis may prove fatal. The period of convalescence is long and it may be six months or more before it is over.

In the laryngeal type mild cases, usually recover in a few days but it may take two weeks before the voice becomes clear. Cases requiring intubation take longer. If only one intubation is necessary the duration is from two to three weeks before the voice is clear. The number of re-intubations required will of course lengthen the duration. Bronchopneumonia is the most frequent complication in these cases and in young children exacts a heavy toll. Paralyses do not as a rule occur.

Complications.—Complications and sequelæ do not as a rule occur in mild cases of diphtheria but occasionally some slight paralysis of the soft palate may be seen. The heart's action, even in the mildest case is affected to some extent manifested generally in tachycardia or irregularity.

In the severer forms, complications are almost sure to ensue and the commonest is some form of paralysis. Palatal paralysis is one of the earliest and manifests itself early in the second week, is gradual in its onset, results in nasal voice and regurgitation of liquids and foods through the nose. It may be slight or the whole structure is completely immobile on phonation. Occasionally it disappears and reappears later in a week or so. It is more noticeable in children than in adults possibly from the fact that regurgitation is more frequent from the nature of their diet. Complete regeneration of the nerve fibers takes considerable time. Paralysis of the ciliary muscle is fairly common. If all cases could be tested it would probably run about 10 per cent. It is usually noted about the third week and adults and older children complain of inability to read when a paper is held about their ordinary reading distance. Occasionally such cases are referred to eye clinics by school inspectors and receive glasses which will be discared in a few weeks when the power of accommodation is restored— as it always is. Strabismus may occur from paralysis of the external ocular muscles, the commonest being convergent.

Paralysis of the facial nerve is very uncommon. The writer has seen only one case in which there was a possibility of its being due to diphtheria. It was slight in extent, occurred about three weeks after the sore throat; the history was very indefinite and the paralysis cleared up in about two weeks. It was unilateral and so far as could be ascertained the only paralysis occurring.

Paralyses of the pharynx and esophagus occur generally around the fourth week, are gradual in onset, cause difficulty in deglutition and even render it impossible in some cases. Gavage is then required sometimes for as long as two weeks but generally only about one week. The inability of the patient to cough up the mucus which accumulates in the throat is very distressing and the danger of aspiration pneumonia is to be borne in mind. Most of these cases recover.

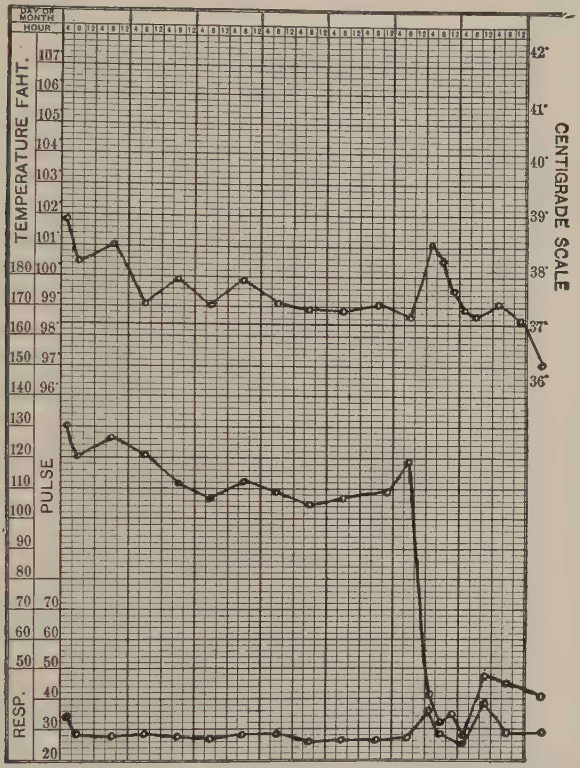

Fig. 6.—This represents a case of this kind. B. L. age four years seven months was admitted to the hospital on the seventh day of illness. No antitoxin had been given. The fall in pulse rate was accompanied by persistent vomiting. Death followed in 36 hours.

Paralyses of the bladder and rectum are very rare. There was one case in the Willard Parker Hospital which showed paralysis of the rectal sphincter. When paralysis of the diaphragm occurs as a result of a lesion of the respiratory nerve, the respiration is costal. Sometimes only one side of the diaphragm is affected. General peripheral multiple neuritis occurs late in the disease—generally the fourth to the sixth week. It may be manifested by weakness of the limbs to complete inability to use them for weeks. In some cases only certain muscles supplied by a nerve are paralyzed and others escape. The muscles of the neck may be so weak as to render the patient unable to hold his head up or the muscles of the trunk so paralyzed that he can not sit erect. He may be so helpless that he cannot feed himself or turn himself in bed.

While the paralysis following diphtheria is generally motor, various sensory disturbances occasionally occur. Numbness and tingling are felt in the hands or feet and may persist for two or three weeks. In all cases with sensory manifestations there is always some muscular paralysis to be found.

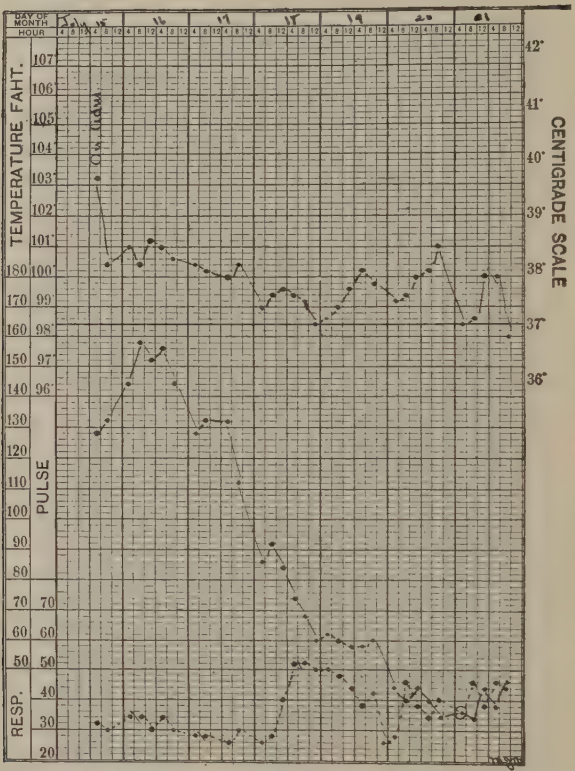

FIG. 7.—This patient age five years had a history of but two days illness. The fall in pulse rate is more gradual than in Fig. 6. but just as marked. It is even less than the respiratory rate. Death on the ninth day of illness.

Heart failure is one of the greatest dangers following diphtheria and may occur at any time. It occurs early in the disease and is manifested by nausea and vomiting and sometimes precordial pain or pain in the epigastrium. The vomiting is generally persistent and cases with this symptom for 24 hours rarely recover. They are mentally clear but somewhat restless and apprehensive. The extremities are cold, the color cyanotic and the pulse weak, feeble and may be imperceptible at the wrist. The heart sounds are toneless and weak and there may be a sudden drop in pulse rate down to even as low as 30 per minute. Occasionally such a case recovers but the vomiting is less persistent, the color better and the heart's action not so weak.

Pulmonary complications are not at all common in any form of diphtheria except the laryngeal. Here it is frequently present, sometimes beginning early in the disease or at a later stage. Occasionally it results from aspiration following paralysis in pharyngeal diphtheria.

Albuminuria is present in a large percentage of cases but it is not of much importance as a diagnostic feature. Nephritis occurs but edema and anasarca as seen in scarlet fever are rarely pronounced. Hemiplegia may occur but is very rare. Loss of knee jerks occurs in a large proportion of cases of diphtheria and may remain absent for several months.

Adenitis of the cervical glands and in severe cases of the submaxillary glands is common. Rarely do they go on to suppuration.

Otitis media has not been a common complication in our experience.

Hemorrhage from the nose is of rather frequent occurrence. Hemorrhage from the mucous membrane of the mouth is not frequent. Rectal hemorrhage has been seen once in a very septic case.

Prognosis.—There are several viewpoints which are to be considered in determining the prognosis in a case of diphtheria, *viz.*, the age of the patient, the type of the disease, the duration of the illness before the administration of antitoxin and the presence or absence of complications. Most of the deaths in diphtheria occur in children from one to five years of age—during the period of greatest susceptibility. The location and the amount of membrane have a decided influence on prognosis, though it is to be remembered that a case with relatively small amount of membrane and called a mild type may develop some dangerous complication and a case with a relatively large amount of exudate and called severe may speedily recover. Speaking generally, the amount of membrane and the structures involved give a clue to prognosis. Cases with membrane limited to one or both tonsils have a favorable outlook. With involvement of pillars and uvula and palate the outlook is more serious. Extension into nasal and post-nasal spaces or down to the larnyx makes the prognosis unfavorable. The greater the amount of membrane with involvement of numerous structures in nose and throat the more guarded the prognosis should be. Marked glandular involvement should be looked upon as evidence of severe infection though the amount of membrane may not be very great. Cases showing hemorrhage either as oozing from the nose or as free epistaxis are unfavorable. Septic cases with petechial hemorrhages in the skin, with waxy pale appearance and dazed apathetic look, generally prove fatal. Occasionally one of these recovers but the chance is extremely small. Laryngeal involvement as extension from the pharynx should be viewed as of serious import. Laryngeal diphtheria causes the greatest number of deaths in the Willard Parker Hospital; 60 per cent. of the cases admitted as croup require intubation. Intubated cases under three years of age do very poorly. Over three years of age the percentage of recoveries is

70 to 80. Bronchopneumonia is responsible for 80 to 90 per cent. of the deaths. Where the membrane is confined to the larynx the patients as a rule do better, even if intubated, than those where the membrane extends to the trachea and bronchi. Cases in which whole casts of the trachea and bronchi are expelled generally prove fatal. Intubated cases with quiet respiration and falling temperature have a more favorable prognosis, especially if the child eats well and sleeps well.

With each day's delay in giving antitoxin the danger from diphtheria increases alarmingly. The attached chart from "Modern Treatment" by Hare shows this very graphically.

MORTALITY FROM DIPHTHERIA AS INFLUENCED BY ADMINISTRATION OF ANTITOXIN

Day of illness	Patients	Deaths	Percentage of mortality
First*	329	5	1.52
Second	2269	77	3.39
Third	2407	165	6.85
Fourth	1612	176	10.91
Fifth	911	136	14.92
Sixth	416	54	12.98
Seventh	320	53	16.56
Later	327	50	15.29
	8591	716	8.33

From Ker's Book on Infectious Diseases.

* In nearly all the fatal cases attributed to the first day, it is extremely probable that it was of much longer duration than was alleged.

Paralyses of various forms are the commonest complications and unless they affect the vital organs, the prognosis is usually favorable. One never knows in these cases with paralysis just when cardiac or respiratory paralysis may occur and so the prognosis should be guarded. Cardiac paralysis usually develops suddenly with vomiting, etc. Persistent vomiting for over 24 hours is extremely unfavorable. A sudden drop in pulse down to 40 or 30 is a very bad prognostic sign. When the pulse becomes imperceptible at the wrist I have seen only one case recover. A pulse which tends to increase in rapidity day to day generally means a poor prognosis. Paralysis of the diaphragm is usually fatal though there are cases reported which recovered.

Diagnosis.—The diagnosis of doubtful diphtheria may be made bacteriologically. It must always be kept in mind that in doubtful cases where there is any suspicion that the case might be diphtheria, antitoxin should be given immediately without waiting for culture report. Again, too, where the clinical picture strongly suggests diphtheria but there is a negative culture report, it is wise to give antitoxin for subsequent cultures will in all probability show the

Klebs-Löffler bacillus. The bacilli which were undoubtedly present at the time of the first culture may not have developed because of unsuitable media or not getting on the swab.

Clinically the diagnosis of diphtheria presents no very great difficulty in the vast majority of cases. Inspection of the throat is usually sufficient, but in young children it is apt to be overlooked as they do not complain of it and it should be a matter of routine for every physician to examine the throat of any child he is called upon to visit.

Follicular tonsillitis is to be differentiated from diphtheria. In this disease the fever is usually higher and the throat is more painful. The tonsils are more enlarged and inflamed. The exudate is yellowish in color, more cheesy and friable and is usually in spots around the opening of crypts. The exudate never extends to the palate or uvula and usually is easily wiped off. The early constitutional disturbance is apt to be greater in tonsillitis. The glands of the neck are enlarged in both diseases.

Vincent's Angina.—In this the exudate is soft, grayish or yellowish-gray in color and comes away in easily torn fragments. The exudate seems to eat the tonsil. It is usually unilateral but may be bilateral. When the membrane clears up there is left a ragged and indolent ulceration. Occasionally it is severer and necroses tonsils, uvula and palate. Antitoxin does not have any affect on it. Bacteriological examination of slides show bacilli and spirilla.

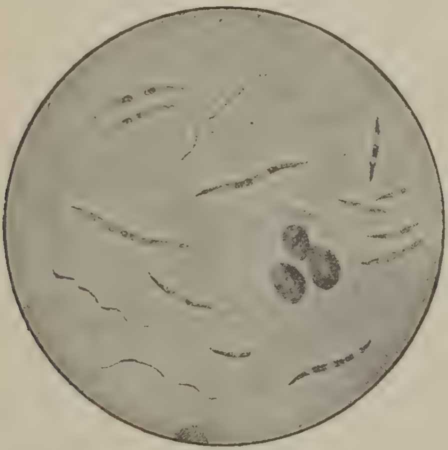

Fig. 8.—Vincent's bacillus with accompanying spirochetes. (Park and Williams.)

Some of the severe cases of diphtheria have been treated as peritonsillar abscess and not been given antitoxin. In abscess there is an exudate which is similar to that of an acute follicular tonsillitis but the swelling usually begins on one side first and the head is held stiff and inclined to the affected side. Salivation is marked and it is very painful to swallow, more so than in any case of diphtheria which might simulate it. There is occasional pain reaching to the ear in abscess and the patient cannot open his mouth nearly as widely as in a case of diphtheria.

The Angina of Scarlet Fever.—In this the exudate is yellowish, soft, pultaceous and easily detached. The throat is very red and there is often a punctate appearance to the soft and hard palate. The mucous membrane of the edges of the uvula when it comes in contact with the swollen tonsils may be covered with thin exudate.

Acute Septic Sore Throat.—The exudate is similar to that of scarlet fever but there is no rash on the palate or on the body. It is generally due to streptococci. Syphilis is not as a rule hard to differentiate from diphtheria. The history of the case, Wassermann reaction culture returns aid in the diagnosis. Post-tonsillectomy cases generally present no difficulty. There is an absence of the tonsils and there is an exudate in the fauces. The history of the case gives the diagnosis but always bear in mind that diphtheria may also be present. In this event the membrane is more firmly attached and organized.

From laryngeal diphtheria, bronchopneumonia is to be differentiated. In it the breathing is more rapid, there is retraction but the dyspnea is not inspiratory. Cyanosis may be present but sweating is not so common.

Retropharyngeal abscess has been diagnosed as croup. This generally is in children under one year of age, with a history of difficulty in nursing and drinking. The head is generally thrown back and there is a characteristic "crow" to the child's cry. Digital examination of the pharynx will reveal a swelling generally to one side of the median line.

Papillomate of the larynx gives loss of voice, retraction and all the other signs of laryngeal obstruction but history shows a very gradual onset over a considerable period of time. Laryngoscopic examination reveals the cause.

Foreign Bodies.—In this the history of sudden onset with violent coughing is suggestive. Laryngoscopic examination should always be made in doubtful cases.

Spasmodic croup is to be differentiated. In this disease, the history shows a sudden onset with absence of fever and hoarseness and a rapid subsidence of the paroxysm; during the day the patient has no difficulty in breathing. The attacks occur at night.

Prophylaxis.—The results of the use of diphtheria antitoxin for treatment and passive immunization were so successful that it seemed justifiable to hope that diphtheria would finally be eradicated. The success attained has indeed been remarkable. Thirty years ago about 150 persons out of every 100,000 living in the middle and New England States died of diphtheria; five years ago only about 21 persons in every 100,000 are victims of the disease. Notwithstanding this improvement, that year 11,455 cases were recognized as diphtheria and reported to the New York City Health Department; of these 1244 cases died. The fact is that while the early gains were very large improvement seemed to have reached its limit. Public authorities seem unable to make the public use antitoxin more generally and more quickly than they now do. The only additional measure that seems profitable is active immunization. Fortunately, there has recently developed a test for identifying persons who are susceptible to diphtheria and also a practical vaccin for immunizing such persons. This vaccin becomes effective in the majority after a few months and gives many years of protection. We will first consider what benefits we have derived from antitoxin and then take up these new procedures. When antitoxin is used as an immunizing agent, its protective action becomes effective in a few hours and continues for an average period of about two weeks. Antitoxin is, therefore, of value when children who are known to be susceptible or who have not been tested as to susceptibility are in contact with a case of diphtheria, and immediate protection, even though of short duration, is desired. In the treatment of diphtheria, antitoxin, when given early enough and in a sufficient dose, has been found to be remarkably successful.

The Limitations of Antitoxin.—As already stated, the injection of antitoxin for immunizing purposes gives protection for a very brief period only. The antitoxin protein which is produced by the horse is not retained by man as if produced by him. To be effectual for protection over a prolonged period, injections of antitoxin would have to be repeated in two weeks and afterwards every week. This is utterly impractical as a general method of permanently keeping the children of a large community immune. The horse produced antitoxin is a foreign protein and is therefore rather quickly eliminated.

So far as treatment is concerned, our present method of using serum has been so improved that we cannot save a larger percentage of our diphtheria cases than we do now. Unfortunately, the therapeutic success of antitoxin is limited because so many fail to realize early enough the seriousness of an attack of diphtheria, and to administer antitoxin without delay. Success in treatment is also limited because of early complicating infections due to streptococcus and pneumococcus, which gains such rapid headway and which render us powerless to prevent bronchopneumonia and other dangerous complications.

Carriers Make the Prevention of Diphtheria Most Difficult.—The chief difficulty in the prevention of diphtheria has been the fact that the number of healthy persons who carry diphtheria bacilli in their throat is so large. In the winter season it has been found that more than 1 per cent. of our population are diphtheria carriers. In other words, there are in New York, during the winter, more than 60,000 healthy persons who, if diphtheria cultures could be taken from the throats of the entire population, would be found to be carriers. It is manifestly impossible to isolate such vast numbers, even if it were not utterly hopeless and absurd to attempt ever to examine the entire population in order to detect all carriers. These carriers transmit the disease in spite of all that has previously been done to prevent it. More than one-half of all diphtheria cases are persons who, so far as can be ascertained, have not been in contact with a known case of diphtheria. One carrier is far less dangerous than a case but there are one hundred carriers to each case. The remedy for this situation is the active immunization with toxin antitoxin. This produces immunity of long duration, or possibly of a permanent character.

The Schick Reaction—Its Significance and Use.—The results of combined clinical and laboratory experience in testing the blood for the presence of antitoxin in cases of diphtheria, and in persons who have been in contact with the disease, have shown that only those individuals contract diphtheria who have no antitoxin or only a minute amount of it in their blood and tissues. Schick, in 1913, published a description of a simple clinical test by which this amount of antitoxin can be accurately ascertained. The reaction depends upon the local action of minute quantities of diphtheria toxin when injected intracutaneously. If antitoxin is absent or present only in very small amounts, insufficient for protection from diphtheria, a positive reaction will appear at the site of injection in from 24 to 72 hours. The Schick test separates the probably non-immunes from the immunes. By it we recognize those who are in danger of infection. To these, when exposed to contagion, we afford protection by prompt removal from contact with the patient, and by injection of antitoxin to evade immediate danger of infection. When these are not in contact with diphtheria they should receive lasting protection through active immunization.

The Characteristics of the Positive Reaction.—A positive reaction is recognized by a circumscribed area of redness and slight skin infiltration which measures from 1 to 2 cm. in diameter. It persists for 7 to 21 days, and on fading shows, as a rule, a superficial scaling and a rather persistent brownish pigmentation. The amount of toxin injected, as advised by Schick, is 1/50 M. L.D. (minimum lethal dose) for the guinea pig, in 0.1 c.c. of normal saline. We prefer 1/50 M.L.D. in 0.2 c.c. It is desirable to give exactly 0.2 c.c., but even amounts, such as 0.1 c.c. and 0.3 c.c., give fairly consistent results—the area of redness being smaller when 0.1 c.c. is given and larger where 0.3 c.c. It is necessary to give it *intracutaneously* so that the toxin will not be too rapidly absorbed but remain in the dense tissue and have time to exert its irritant action. The slightly raised white area, at the point of injection, is infallible evidence that the diluted toxin has been delivered intracutaneously. In infants under one year 0.1 c.c. is sufficient, but it is safer to give 0.2 c.c. If the toxin escapes into the subcutaneous tissues the reaction usually takes place but it is not so certain.

The Characteristics of the Pseudo-reaction.—Shick noticed that, in the older children and adults, a considerable percentage showed a protein reaction which had nothing to do with the specific toxicity of the toxin. In these cases, even when the mixture was over neutralized with antitoxin, this same pseudo-reaction developed. In most cases, this reaction came on more promptly, covered a larger surface, was more of the urticarial type, had as a rule a more reddened central area and a lighter surrounding zone, and disappeared within two to four days. Pigmentation is absent or slight, and superficial scaling is very rare. In a small percentage, however, the reaction persisted for a week or 10 days and it was very difficult in many and impossible in some to decide between a true and pseudo-reaction. When there was a combined reaction it was even harder to decide how much, if any, was due to the toxin and how much to the non-toxic protein, because the development of a true reaction in no way prevented the protein reaction. With a pronounced pseudo-reaction there may be a slight rise in temperature.

Control Tests.—The best practice, therefore, in older children and adults is to inject the toxin in the skin of one arm, and the heated or antitoxin neutralized toxin in the other arm. In this way the amount of protein reaction can be noted, and it can be decided whether the reaction following the toxin is a simple, true reaction, a pseudo-reaction, or a combined reaction. Even after the eye has been thoroughly trained, it is still wise to use the two injections when possible. On other occasions, when only one injection is made, any cases which remain in doubt are considered as true reactions and treated accordingly.

Details of the Technique.—I think it is apparent to all that the technique of the Schick reaction, although very simple, must be carried out with the greatest accuracy, or the results will be frequently misleading. If the toxin has been diluted and stored in a warm place, *it may readily deteriorate* and, instead of giving 0.02 of a fatal dose (M.L.D.) only one-half that amount may be injected, and no toxic reaction will occur, and the misleading idea is given that the person has been shown to be immune. Several years ago Dr. Zingher tested the outfits from five plants producing biological products and found that a considerable percentage of the outfits received from three of these gave inaccurate results. In one case two of the five outfits tested gave negative results in children having no antitoxin. It was found that much of the glass used to make the vials and capillary tubes caused the toxin to deteriorate. This error has since then been corrected. If the toxin is incorrectly diluted, and a large surplus of toxin is given, slight necrosis may develop at the point of injection. On two occasions when the test was extensively employed, elsewhere in New York state, this accident occurred and some hundreds of people received undiluted toxin and developed very sore arms. The neutralized or heated toxin, used for the pseudo-reaction, must also be prepared with care.

To carry out the test, it is essential to have an accurate syringe, with a sharp, but short-pointed, fine needle. Most persons prefer a needle with a length of 3/8 in. The usual 1 c.c. "Record" tuberculin syringe, with a fine platinum-iridium needle, answers the purpose well. The Research Laboratory places a standard diphtheria toxin in capillary tubes in such amount that the contents of one added to 10 c.c.

of water gives the required dilution. The dilution will keep in the icebox with little deterioration for at least one day. When bulk toxin alone is at hand, further dilutions are made in normal saline, of such strength that 0.1 or 0.2 c.c. contains $\frac{1}{50}$ M.L.D. for the guinea pig. As already stated, Schick prefers a bulk dose of 0.1 c.c. while we prefer 0.2 c.c. This amount is injected, intracutaneously, on the flexor surface of the arm or forearm. The persistent pigmentation for several weeks which often results may make selection of the forearm in women slightly objectionable.

Interpretation of Reaction.—Though the intensity of the reaction varies in different individuals, as well marked persisting redness indicates an almost complete absence of antitoxin in the individual tested. Faint reactions lasting three to seven days point to the presence of very small amounts of antitoxin, which are not sufficient, however, to certainly protect the individual against diphtheria, but are sufficient to protect from systemic intoxication. To prevent the appearance of the reaction, according to Schick, the presence in an individual of at least $\frac{1}{30}$ unit of antitoxin per c.c. of blood is required. With the weaker dilution we employ $\frac{1}{50}$ unit will prevent a reaction. According to v. Behring, even as little as $\frac{1}{100}$ unit of antitoxin will protect against the disease in uncomplicated cases. In a child three years of age, weighing 35 lb., we found that a subcutaneous injection of 10 units of antitoxin were sufficient to prevent the appearance of the Shick test when made 24 hours after the injection of antitoxin.

The Practical Value of the Schick Reaction.—The Schick reaction has been carried out by us, during the past ten years, on all patients entering the scarlet fever pavilion of the Willard Parker Hospital. Only cases giving positive reactions were immunized against diphtheria; those giving a negative reaction received no immunization, but were carefully observed. Although many of the negatively reacting patients become carriers of virulent diphtheria bacilli during their stay in the wards, no cases of clinical diphtheria developed among them. The patients who gave positive reactions received, in practically all cases, injections of diphtheria antitoxin. Previously to adopting this practice of giving antitoxin about 6 per cent. of the cases developed diphtheria.

The percentage of individuals susceptible to diphtheria is shown by the Schick test to be greatest between the ages of one and two years. It is much greater in the country than in the city. It is less during the second six months of life, and less in older children, and least in adults and infants under six months. In adults, the positive reactions were not more than 20 per cent. on the average. In different institutions and in people from different races and localities quite different percentages were obtained.

During systematic testing of groups of children belonging to families, we have been impressed with the frequency with which all the children of the same family gave a similar reaction. If variations were found, the younger children, with the exception of the baby, always gave the positive reactions. If the youngest child had a negative reaction, all the older children were also negative. On the other hand, if the oldest child in a family gave a positive reaction, the younger children always showed positive reactions.

Susceptibility of Various Ages to Diphtheria
(As indicated by test in over 30,000 persons)

Age	Average positive Schick, per cent.	Schick range positive	
		Cities	Country
At birth	15	10	25
Under 4 months	15	10	25
4 to 6 months	30	25	35
6 to 9 months	70	60	85
6 months to 1 year	80	65	90
1 to 2 years	75	60	90
2 to 3 years	65	50	80
3 to 5 years	40	15	70
5 to 10 years	35	8	65
10 to 20 years	30	5	60
Over 20 years	30	5	55

Permanence of Negative Reaction in Persons Developing Natural Immunity.—The value of the Schick reaction as a practical guide in judging the immunity of persons depends on the duration of this condition. If natural immunity developed in children lasted only a few weeks or months, the value of the Schick test would be in the immediate emergency of an outbreak of diphtheria when sufficient time was available to make the test in order to inject antitoxin or separate from danger those who showed a positive reaction. If, however, a child or adult developing natural immunity holds that immunity for life, the knowledge that it gives a negative Schick reaction is of value, not only for the present, but for the rest of the individual's life time. For the past eight years, we have been testing and re-testing thousands of children and hundreds of adults and keeping records. We found that, with few exceptions, that those who gave a negative Schick test continued to show immunity during the years. From this and the fact of the age distribution of immune children in families in which the younger have a positive reaction and the older children and adults a negative reaction, it would seem that when once a child develops natural immunity this is a usually lifelong possession. It is true that we have found, during the eight year period mentioned, an annual change in about 3 per cent. of the cases noted to have had a negative Schick reaction to a positive reaction. It is my belief that all of these supposed changes in reaction are not actual but that some are due to improper material or poor technique in making the intracutaneous test or in the reading of the reaction. More careful observations in the future will show whether this opinion is correct or not. Although the lapse of natural immunity or variation in its amount is so infrequent it is wise to re-test young children or older persons who have just been or expect to be in direct contact with diphtheria if more than three months had elapsed since the test. I know of one nurse and one sailor who contracted a moderate diphtheria seven and nine months after an apparently negative Schick test. Six weeks after recovery the nurse showed a positive reaction.

A matter of much practical importance is whether a person with sufficient antitoxin to give a negative reaction has sufficient to prevent the development of diphtheria. We have been so in the habit of considering that a positive culture on Löffler's blood serum indicated that the suspected case had diphtheria, that we have lost sight of the true fact, which is that such a culture simply indicates that the case is a carrier. By tests we know that the bacilli found in many are absolutely non-virulent. It is also an undoubted fact that a person who is a carrier of virulent or non-virulent diphtheria bacilli may be afflicted with a septic tonsillitis, due to the streptococci or other microörganisms. When a case of doubtful diphtheria has a negative Schick test and a positive culture, it is extremely difficult to decide how to consider the case. From the practical standpoint, antitoxin should be given if the case is at all serious because there is always a possibility that there has been some error in the technique of the test, or in its reading, or some mistake as to the identity of the individual. From the scientific viewpoint, the matter is of special interest. During the ten years we have used the Schick test, no cases of severe diphtheria have developed in persons known to have had a recent negative Schick test, while some 12 cases of moderate tonsillar infection with at least the presence of diphtheria bacilli have been observed in such individuals.

In most of these cases, no antitoxin was given, and recovery took place as quickly as in those receiving it and as in similar cases of doubtful diagnosis in which no diphtheria bacilli were to be found in the cultures. In an adult who had given a negative Schick test 11 months previously a characteristic moderately severe case of diphtheria developed. This is the only undoubtedly true case that I have personally encountered. It seems safe to rely on the belief that a person with a sufficient amount of antitoxin to give a negative Schick test is incapable of developing constitutional toxemia, or a severe local infection from diphtheria bacilli. There is a doubt as to whether very slight infections of the superficial mucous membrane may occur in borderland persons. My own opinion is that the great majority of cases supposed to be of this character are instances of strepto coccus infection, the diphtheria bacilli if present being there as in a carrier. Those that show a faintly positive Schick test are liable to moderate local infections. Careful observations of these persons with faint reactions will allow us, in time, to decide whether they require immunization. If this is given, it should be produced by antitoxin for the immediate danger, and by toxin-antitoxin for later and permanent effect. It takes from five to six weeks to develop active immunity by the use of toxin-antitoxin. My own opinion is that except in the case of nurses who export to heat diphtheria, it is not necessary to inject these faintly positive cases.

The property of diphtheria toxin partially neutralized by antitoxin after injection in animals to produce antitoxic immunity became known to a number of investigators in 1895 and 1896 through attempting to use test animals that had recovered from the effect of slightly underneutralized test mixtures of antitoxin and toxin. Wernecke in 1895 reported that even fully neutralized toxins were effective for this purpose and that the young of these immune animals also possessed antitoxin immunity. In the following year I duplicated his results. Dreyer and Madsen in 1901 produced through similar injections in horses and goats serum of very considerable potency. The observations of Rehme on rabbits when added to those of other observers developed the fact that animals which have traces of antitoxin naturally respond in a few days to the stimulus of the neutral mixtures, while those which have none require four to six weeks. The guinea pig and rabbit have no natural antitoxin while the horse and the goat usually possess it.

In 1905 Theobald Smith suggested in a publication that human beings might be immunized, but the time was not ripe. Experimental bleedings had demonstrated that two-thirds of infants beyond the age of nine months possessed no antitoxin, but there was no way to detect those that were susceptible except through bleedings and no method to determine the result of injections except by the same troublesome method. The introduction of the Schick test for antitoxic immunity by the intracutaneous injections of minute doses of toxin completely altered conditions. It became immediately practicable to test large numbers of people, so as to detect those having no antitoxin and to watch what changes if any followed toxin antitoxin injections. Behring and some of his associates were the first to attempt to immunize human beings with the neutralized toxin. His results were published in May, 1913. These, while very incomplete, were on the whole favorable. We began to use the human injections immediately after Behring's report. The most important problems to be worked out were the exact degree of neutralization of toxin by antitoxin which would be most effective, the number and amount of the injections, the time of appearance, the extent and the duration of the immunity, the effect on the immunizing response to the vaccin of giving a simultaneous injection of antitoxin in another portion of the body, the reaction of the tissues in persons of different ages, the response in infants who are passively immune through the transfer to them of antitoxin from their mothers, and finally the degree of local and constitutional protein reaction necessary.

The best degree of neutralization was tested out by trying different mixtures in guinea pigs and horses.

The results of a great many experiments convinced us that a mixture that had sufficient antitoxin added to just rob the toxin of any acutely poisonous effect even when given in large doses was as effective as one that was more toxic. Although in the amount that it is given a mixture which would be slightly toxic in large doses in a guinea pig would be perfectly safe in an infant, it is nevertheless a great satisfaction to be able to use an effective almost non-toxic product. A useful point in the manufacture of the product is that a moderately toxic mixture before filtration through a stone filter is just suitable for use after such treatment. It is not well to overneutralize the toxin since the product becomes less and less stimulating of the production of antitoxin, as the excess of antitoxin increases. The size of the injection; this was tested in different animals and in man. It was found that moderate doses gave considerably better results than small doses. When the amounts given were greatly increased some additional response was noted, but not sufficient to make it wise to risk in man the objectionable protein reactions which develop in a certain proportion of persons injected. We, finally, decided on a 1 c.c. dose of our standard toxin when it was possible to give three injections. The toxin used had a minimal fatal dose of about 0.0025, and an L+ dose of about 0.40. A somewhat weaker or stronger toxin could equally well be used if the amount of fluid was adjusted proportionately. The local reaction is due almost wholly to the autolyzed bacillus substance and other proteins in the culture fluid which are not related to the specific toxin. Attempts to remove these undesirable substances have already been partially successful. The number of injections: Each added injection gives an additional antitoxin response. For practical purposes it is necessary to restrict the number to as few as possible. This therefore has to be worked out by observations on human beings. Many hundreds of tests have demonstrated that from one injection we may expect at the end of three months about 60 per cent. of positive Schick persons to develop enough antitoxin to change to negative test. Two injections will change about 75 per cent. of the positive Schick cases and three about 90 per cent. If a second series of these injections are given to the refractory cases about 80 per cent. of the resistant cases will respond. Even this remainder of 2 per cent. can be immunized by further injections. At the end of six months a somewhat larger percentage of negative cases will be found. Under different conditions one, two or three injections may be desirable. We try to give three when possible, but often have to be satisfied with two or even one.

The time of the appearance of the antitoxin: A very interesting discovery was quickly made that warm blooded animals which have traces of natural antitoxin produce very considerable amounts within five to seven days, while those which have none require from 4 to 12 weeks before appreciable amounts accumulate in the blood. The antitoxin content of the blood in immunized horses drops back to the original amount, in about nine months. Some human beings have and some have no natural antitoxin; there are therefore among them those which respond quickly and those which respond slowly. The interesting fact developed that while those receiving injections which previously had antitoxin dropped, as the horses, in a year to their original amounts, those that had none continued to remain immune for about two years.

The late development of antitoxin in those having a positive Schick test impresses the truth that toxin-antitoxin cannot take the place of injections of antitoxin when there is immediate danger of infection. Diphtheria antitoxin gives immediate and absolute immunity for a short period. Toxin antitoxin develops immunity after a lapse of from one to three months and for a long period. Each therefore has its important part in the prevention of diphtheria and one supplements the other.

The Park Modification of the Schick Test.—It was discovered by Park that a subcutaneous injection of 1 c.c. of the standard toxin-antitoxin mixture would give the same reaction as the Schick test. The advantage is that there is made at the same time an immunizing and a diagnostic test. The anterior part of the lower arm is the most satisfactory point to make the injection. It should be injected just beneath the skin. The toxin-antitoxin mixture used should kill a guinea pig in a 5 c.c. dose. It is very useful in children. In adults the pesudo reaction is confusing.

Bactericidal and Antitoxic Immunity.—Immunity to diphtheria may be due to the presence of antitoxin or of bactericidal substances. The majority of those who recover from diphtheria have not developed at the time any appreciable antitoxin. We discovered this by testing convalescent cases that had recovered without antitoxin treatment. The immunity developed from the toxin-antitoxin injections is almost wholly antitoxic. If sufficient antitoxin develops, it is as effective as a larger amount.

The Duration of the Immunity.—This can only be determined after the lapse of years as the first to be immunized still possess antitoxin. No reports have been received from the persons receiving the first injections in Germany. Our observations, therefore, extend over the longest period of time. These are upon positive children in institutions which were immunized by Doctor Singher from six to eight years ago. He tested the results after one and two years. In his absence during the period of the war and since his return Doctor Schroder tested them. Each year some of the children leave the institutions and are lost track of, so that the figures on the cases observed for three years or longer are rather small. Fortunately, the results are so similar in the different groups that we can probably safely rely upon the moderate number of observations. It is remarkable how well the immunity persists. There has been almost no change from year to year. It appears as probably that the vaccin has not only stimulated a production of antitoxin, but has aroused the cells to an activity which had before remained dormant, so that these persons who before made no antitoxin join the larger group who normally produced it. There is so far as I know no explanation of the making of natural antitoxin. The fact that it develops in the children of most families at a certain age and that it is present in the great majority of horses and many other animals makes it difficult to assume that it is necessarily due to the stimulus of diphtheria bacilli, present in the throat without producing disease and therefore undetected.

The effect of giving in different portions of the body antitoxin and toxin-antitoxin simultaneously. The fact that in man and in animals the members that have antitoxin present in their bodies react to the toxin-antitoxin injections is sufficient proof that antitoxin in the circulating fluids does not wholly prevent injection of toxin-antitoxin from stimulating additional antitoxin.

Horses as they accumulate antitoxin during immunization continue to receive stimulus from continued injections of toxin. It is true, however, that larger amounts are required to exert the necessary effect. The presence of antitoxin lessens therefore somewhat the effectiveness of the stimulus of an equal amount. We have not made sufficient observations on young infants to be certain of the degree to which the presence of antitoxin diminishes the response. That it has some effect is clear. Given after the toxin-antitoxin it has no inhibiting effect. The following two institutions are very interesting. In one the antitoxin was given at the same time as the first injection, in the other simultaneously with the second injection. In the former case a considerable inhibition of the development of antitoxin was apparent, while in the latter the antitoxin had little if any retarding effect.

The Reaction at Different Ages.—The baby of an immune mother is immune because of the passive transfer of antitoxin as well as other antibodies. Sometime during the first year it usually completely eliminates the mother's antitoxin. Later as a rule its own cells develop it. The infant may differ from an older child in another way. Besides having antitoxin from its mother, its cells may not yet have acquired the ability of producing antitoxins. Infancy is the time of life at which we would like to immunize because diphtheria is chiefly a disease of the early years of life. The problem to solve as to the earliest age that practical immunization can be carried out is therefore a very important one.

Four years ago we injected 2100 infants on the third, sixth and ninth days after birth. After a lapse of 12 months we have re-tested them. The results were quite disappointing. The percentage of immune children was no greater than in those in whom no treatment had been given. We have immunized many non-immune infants of an age from six months to one year and have found them as readily immunized as the older children. The degree of local and constitutional reaction to the injections: Our observations have convinced us that the reactions are due partly at least to the proteins other than the toxin. The protein reaction is absent in the newly born, infrequent in the young child and more frequent in the older child and adult. There may be a reddened and slightly painful area of several inches in extent. The reaction is much less with the new preparation of toxin-antitoxin which we developed more than a year ago and have used since. The protein in this is only one thirtieth of that in the old mixture. This is technically called the one-tenth L+ preparation. Not a single child among the last one hundred thousand injected has developed the slightest infection or any lasting harmful results. During the past four years the health inspectors alone have Schick tested more than 500,000 children and have given those who developed a positive reaction these injections of toxin-antitoxin. In no case has any serious deleterious effect been noted. The deaths have declined each year and in the four years have dropped from 1200 to 570. This improvement is undoubtedly due partly to the active immunization of the children with toxin-antitoxin and partly to the earlier use of antitoxin.

Antitoxic and Medical Treatment.—In the treatment of diphtheria antitoxin holds chief place. Statistical proof has abundantly established its great value in reducing the mortality from the disease. But its limitations should be recognized. It cannot undo damage already done and to have its greatest effect must be given early in disease, before the toxin has been able to exert its poisonous effect on the tissues. Only one dose is indicated but that should be of an adequate amount.

The serum may be administered either subcutaneously, intramuscularly or intravenously. As the rate of absorption is slowest from a subcutaneous injection it is advisable to limit this method to the very mild cases, while in the severest forms the intravenous method should be employed. The most suitable site for intramuscular injection is in the anterior surface of the thigh about its middle third, as in this location the patient is less inconvenienced. The dosage will depend on the severity of the case and its size. For mild cases, 3000 to 5000 units, for moderate cases, 7000 to 10,000 units, for severe cases, 15,000 to 20,000 units and septic cases, 30,000 to 50,000 units may be given.

In severe and septic cases the use of the intravenous method is strongly urged. One unit given intravenously is worth ten given intramuscularly and twenty given subcutaneously. The following doses may be given in young children intravenously: Laryngeal 3000 units, severe and septic cases 7000 to 10,000 units. In adults these doses should be doubled. Many have hesitated to employ this method on account of the severe reactions that occasionally follow. In children under six years it is rare to meet with symptoms more alarming than a moderate chill, while the greater number suffer no reaction whatever. In children four years and under seven chills were noted in 105 injections. Although adults occasionally have severe chills accompanied by nausea and vomiting, these considerations should not outweigh the great advantages that are to be gained. Care must be taken if intravenous injections are given insensitized persons. In uncomplicated cases the results are frequently striking. There is an early fall in temperature and pulse, accompanied by a marked improvement in the well being of the patient. Headache and general malaise disappear rapidly. We have rarely seen any further extension of the membrane and the edema subsides more promptly than under any other form of treatment. Even in septic cases there is usually an early drop in pulse rate although the fall in temperature is as a rule more gradual. In the laryngeal form the results are not so marked as here pulmonary complications are very frequent. Our experience, however, has been that if this method were employed on the first day that the symptoms appear fewer cases would come to intubation.

To avoid the occasional unpleasant reactions that result from the intravenous injection of the ordinary commercial antitoxin we have been using only a highly potent product, diluted to twice its volume with normal saline. The precipitate which gradually forms on standing is removed by filtering. By this means much of the untoward reactions have been eliminated. In one series of over 1800 cases but six chills have been observed, one in a boy five years old, very mild in character, and the remaining in young adults, moderately severe. Since then we have had a somewhat greater number of serum reactions.

Technique.—A good syringe and needles of proper size are prime essentials for successful work. We have found a Burroughs and Welcome 5 c.c. most satisfactory. An added advantage of this syringe is that the appearance of blood in the lumen of the end-piece—an indication that the needle is in the vein—is readily seen. Two sizes of needles are used, a No. 9 of the above firm or a No. 19–1½ in. Luer for injections into the jugular vein and a No. 22–1 in. Luer for the arm. The serum should be at body temperature. Scrupulous asepsis should of course be observed throughout.

Before administrating the serum ascertain whether the patient has had previous injections of horse serum or is subject to asthmatic attacks, in which case the procedure should follow the lines indicated below.

In older children and adults the median basilic vein is the best site of injection and can usually be found without much difficulty. To prevent struggling in younger children it is best to "mummy" them as described under intubation, leaving one arm exposed. Often the veins in the arms of small children can neither be seen nor palpated. The external jugular can be then used.

In this case the child is laid on his back and "mummied." The nurse with one hand on the forehead and the other on the occiput turns the head to one side, at the same time depressing it, thus bringing the vein into view and tightening the skin over it. If the injection is to be made in the left side the operator stands on the right, and *vice versa*, the direction of the needle thus naturally lying in the course of the vein. Usually the vein is quite prominent. As the needle is inserted into the skin, the crying of the child causes them to swell out when they can be entered without difficulty.

There seems to be a general reluctance to administer antitoxin, where there is a history of injections at some previous period, lest the patient prove anaphylactic. While this is theroretically possible the event must be exceedingly rare. We have had no bad results when the second injection is given intramuscularly. If the case is one of sufficient severity to warrant the intravenous method it is best to wait two or three hours after the subcutaneous injection and then inject 0.1 c.c. intravenously. If no reaction results in 10 minutes the full dosage may be given if it is given very slowly. If the case is very severe the antitoxin should be given intravenously without waiting to make the attempt to lessen the serum sensitiveness. It should under these circumstances be given very slowly and stopped immediately if any untoward symptoms develop. The remainder of the antitoxin should then be given intramuscularly.

If there is a definite history of asthma it is advisable to first test the susceptibility of the patient with a subcutaneous injection of 0.1. c.c. of serum. This may be repeated every 15 minutes until 0.5 c.c. are given. A similar amount may then be given intravenously followed by the full amount, if no untoward symptoms appear. Should anaphylactic symptoms appear atrophine may be tried.

Local Treatment.—In the majority of cases none is needed. Where there is marked swelling of the peritonsillar tissues with excessive amount of mucus a gentle irrigation with saline or soda bicarbonate (1 dr. to 1 pt. of water) is beneficial. Care should be taken not to use force. Irrigation of the nose is not recommended as there is a tendency for infection to be carried upward with resulting middle ear disease.

Diet.—The diet should be as nourishing as possible. Liquid foods such as milk, broths, beef juices and egg-noggs should be given in the first few days of the disease. Where milk is not well borne it may be diluted with Vichy or lime water or flavored with coffee or cocoa. Cereal gruels may be added with advantage. Jellies, custards, junket and soft boiled eggs in the milder cases can be given from the first and in more severe cases towards the end of the first week. Gavage may be necessary where paralysis of the esophageal muscles is pronounced. Occasionally the throat may be so swollen in septic cases as to render swallowing impossible and rectal feeding must be resorted to.

Complications.—For the various forms of paralyses complete rest in bed is essential for at least one week after all symptoms have disappeared. Even in mild cases where only the soft palate is affected this rule should be adhered to as it is impossible to say whether severer forms may not develop later. Rarely the esophageal muscles may be so involved as to render gavage necessary. When the diaphragm is affected the mortality is very high. Atrophine and strychnine may be tried. In cases of multiple neuritis strychnine, electricity and massage have been recommended. For the anemia which is usually present some iron preparation such as the Syr. Ferri Iodi may be given. It is questionable, however, whether these measures have an effect in hastening recovery. Fresh air, a nourishing diet and careful nursing will probably accomplish all that is possible.

Where there is serious cardiac involvement extreme care is imperative. The patient should not be allowed to sit up in bed or feed himself. Where there is restlessness morphine should be given in sufficiently large doses to insure quiet. If delirium is present a tepid sponge bath or alcohol rub has a soothing effect. The various cardiac stimulants, caffeine, digitalis, etc., may be tried but in our experience they have proved very unsatisfactory. Epistaxis, which is not uncommon in the severe and septic cases, frequently proves very obstinate to control. Usually it is of the nature of a continuous oozing which is extremely difficult to check. Thromboplastin may be applied locally. (In the more persistent forms plugging of the posterior nares may be necessary.) An intramuscular injection of 20 c.c. of normal horse serum should be tried or better 30 c c. to 50 c.c. of citrated blood from one of the parents.

For the distressing pruritus which occasionally accompanies the urticarial rash the injection of 10–15 M. of 1:1000 adrenalin solution hypodermically sometimes proves very efficacious. When this fails any antipruritic lotion may be used. Equal parts of 5 per cent. phenol and 75 per cent. alcohol gives great relief.

Convalescent Period.—There is no disease so treacherous as diphtheria. Even when the patient seems to have completely recovered a fatal termination may result from cardiac or respiratory failure. A rapid pulse, a varying pulse rate or one that shows a pronounced increase on slightest exertion, such as sitting up for an hour, is evidence that recovery is not yet complete even though no other symptoms are present. While these signs persist the patient must be confined to bed. A paralysis may develop after mild cases especially if antitoxin has been given late in the disease. Where the disease has been of an unusually severe form the patient should be confined to bed for five or six weeks, although his general condition is excellent, as multiple neuritis usually occurs about this period. For the next two to three weeks care should be taken to avoid undue exertion. It is much better to err on the side of safety than to be taken unawares by some fatal complication.

Complications such as bronchopneumonia, otitis media and nephritis should receive the same treatment as when due to other causes.

Diphtheria Carriers.—Considerable annoyance is sometimes caused by the persistence of the diphtheria bacillus in the throat after convalescence. Treatment with local applications of various antiseptics has proved very unsatisfactory. For several years it has been the custom with us to perform tonsillectomy in all cases persisting longer than three weeks. This operation has proved by far the most successful treatment. If laboratory facilities are available, the organism may be tested for virulence.

Cleansing non-irritating solutions like normal salt solution may be used to cleanse the nostrils and the throat. If possible the patient should sit or play in the sunshine a part of each day. Everything which will tend to make the mucous membranes of the nose and throat more normal and which will improve the general health will tend to hasten the disappearance of the bacilli.

CHAPTER CXLII

LARYNGEAL STENOSIS, INTUBATION, TRACHEOTOMY

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The term "laryngeal stenosis" in its broadest sense is applied to any condition which so narrows or constricts the lumen of the larynx or upper trachea as to interfere with the free passage of air. In this broad sense it will include constriction due to pressure, as from tumors outside of the larynx or trachea, and foreign bodies lodged within the air passages. In a more restricted sense it applies to conditions resulting from pathologic processes (systemic or local) producing edema (renal, irritants, anaphylaxis, extension of inflammation), spasm (croup, laryngospasm), new growths within the larynx (papillomata) and false membrane. The most common of these, and therefore the most important, is membranous croup or laryngeal diphtheria.

Each condition causing stenosis or symptoms resembling stenosis will be discussed briefly, and the diagnosis from laryngeal diphtheria emphasized.

Pressure from Without.—Mediastinal tumors are unusual in early life, yet they occur with sufficient frequency to be kept constantly in mind in diagnosing any case of difficult or obstructed breathing. Large masses of tuberculous lymph-nodes are by far the most frequent variety though more rarely a malignant tumor either primary or secondary to a growth elsewhere in the body may be present. A tumor in this region may develop in the course of Hodgkin's disease. These two latter conditions are rare and are usually accompanied by other symptoms of the concomitant disease. Masses of tuberculous nodes usually accompany pulmonary involvement, but they may be present when there are lesions in other parts of the body, or they may be the primary seat of the disease. In some instances the other involvements may make the diagnosis clear, but other symptoms may be so slight as to pass unnoticed.

Respiratory symptoms from such masses, which are rarely seen prior to the third year of life, are dependent largely on pressure, their intensity depending on the size of the mass. This pressure may be exerted on the trachea or large bronchi, or on the pneumogastric or recurrent laryngeal nerve. When the air passages are encroached on the lumen is narrowed, and there may result a gradual but steadily increasing stenosis. This, however, is not always so for there may be marked intermissions, the attacks becoming paroxysmal at times. Expiration is usually more difficult than inspiration. When the cause of symptoms is pressure on or irritation of the pneumogastric or recurrent laryngeal nerve, spasmodic cough is the rule, with dyspnea and change of voice usually present also. The case may so closely resemble spasmodic croup as to render a diagnosis difficult. Ulceration of the diseased nodes may take place into the trachea, allowing the escape of the gland into the air passages. It may then be expelled by coughing, or remain in this location and cause symptoms which are identical with those of an aspirated object. If an abscess has developed and ruptures into the air passages sudden death may result. Diagnosis of these conditions may present considerable difficulty; in some cases the aid of the *x*-ray is indispensable. If the attacks are spasmodic and of short duration membranous croup can be ignored in the diagnosis; if they are prolonged the diagnosis is not so easy. The possibility of death occurring during the first attack must be borne in mind.

An enlarged thymus gland often gives rise to paroxysmal attacks of asphyxia, which closely resemble laryngeal stenosis. These attacks may or may not be accompanied by convulsions. An enlarged thymus may also so press on the trachea as to cause gradually increasing symptoms of stenosis. The paroxysmal attacks may not be due to pressure of the gland on the air passages, but are more apt to be manifestations of the little understood status lymphaticus. Diagnosis is made by percussion of the area of thymic dullness, palpation of the gland in the suprasternal notch, and by the *x*-ray. All of these methods are signally uncertain. Direct bronchoscopy reveals the absence of membrane and may disclose a curved narrowing of the lumen. Where pressure from the enlarged gland can be clearly demonstrated tracheotomy may help as may also the long tracheobronchial tube of Lynah, introduced by direct bronchoscopy.

Foreign Bodies in the Larynx, Trachea or Bronchi.—The lodging of foreign bodies in the air passages is a rather frequent accident. The symptoms depend on the size and shape of the body and its location in the larynx, trachea or bronchus. The character of foreign bodies varies greatly; buttons, safety pins, screws, nails, popcorn and peanuts are examples. A large body lodged in the upper respiratory tract may suddenly cause symptoms of severe asphyxia, while a smaller body or one long and slender, passing at once into a secondary bronchus, may remain for years without noticeable symptoms, and later cause infiltration closely resembling a chronic pneumonia or a tuberculous lesion. Usually sudden coughing at the time of aspiration occurs. Lung abscesses are not an uncommon sequel. Between these two extremes all degrees of obstruction occur. A foreign body in the trachea or large bronchus, of such size (grain of corn or peanut) as to partially obstruct respiration, usually causes a peculiar wheezing, high-pitched sound, with or without rattling. There may be just enough obstruction to bring the accessory muscles of respiration into play, and to one who has not seen many such cases, the sound closely resembles the breathing of membranous croup. It is, however, quite characteristic when often heard. The symptoms may be continuous or spasmodic. Often there is difficult breathing with prolonged attacks of coughing, both with and without cyanosis. The obstruction to respiration is apt to be inspiratory, though both inspiratory and expiratory dyspnea may be present, as in those instances where the foreign body is so situated that it moves with breathing and acts as a flap or a ball valve. In many instances the exact location of the obstruction may be demonstrated under the stethoscope, whether in the trachea or in a bronchus, when there is found a peculiar hissing respiratory note, and beyond this point a changed character of breath sounds. Percussion beyond the obstruction usually shows dullness. If the object is made of mineral or metal the *x*-ray will disclose it at once; if of vegetable matter, usually no shadow is cast, although on very close observation we can sometimes discover a very faint shadow. Many buttons are made of celluloid or similar substances which cast no shadow under the *x*-ray.

Tonsils, Adenoids and Enlarged Cervical Glands.—While not strictly belonging to the conditions classified as laryngeal stenosis it may not be out of place to consider the obstructive symptomatology of this group of tissues. As is well known, tonsils may be so large as to meet in the mid-line of the pharynx. Such enlarged tonsils are usually associated with exuberant growth of adenoid tissue. This is accompanied by uncomfortable, if not serious, obstruction to breathing. When these tissues are actually inflamed the congestion and swelling may become serious. When this occurs and is accompanied by excessively large infected cervical glands (as is often the case in rhinopharyngitis, influenza and scarlet fever) the difficulty in breathing may be so great as to necessitate the aid of the accessory muscles of respiration, and present a picture closely resembling membranous croup. The possibility of an intercurrent diphtheritic infection must not be lost sight of. During outbreaks of severe infection this picture is not at all uncommon.

Retropharyngeal abscess is the result of suppuration of infected lymph-nodes on the posterior wall of the pharynx on each side of the cervical spine. The condition is usually unilateral and is seen on one side or the other of the mid-line. If the chain of glands on both sides of the spine are infected at the same time the mass may appear to be centrally located. The inflammation of the glands alone may cause symptoms of obstruction to either respiration or deglutition, or both, but by far the most frequently observed condition is the formation of an abscess from the suppuration of these glands. The constitutional symptoms may be mild or severe. When severe there is high fever and prostration, usually out of proportion to discoverable cause. By continual observation the swollen mass will be seen to partially or completely obstruct the pharynx or post-nares. Gradual interference with deglutition or respiration may be the first intimation that anything is wrong. The obstruction to respiration—which is inspiratory—may be extreme, nasal respiration being first interfered with, while in some instances, especially if the abscess is low in the pharynx, deglutition becomes extremely difficult. This condition is more often mistaken for membranous croup than for any other condition; so much so, in fact, that both intubation and tracheotomy have been performed for its relief when a careful examination has not been made. The child usually extends the head in an effort to obtain relief. Local symptoms are usually gradual in onset. Direct inspection may be sufficient to discover the cause of the trouble, but by far the surest method is digital examination. Usually a boggy mass is felt, partially filling the pharyngeal opening, but is more pronounced on one side than the other. A mouth gag should never be used, since symptoms of asphyxia may be induced, and even immediate death has been known. An abscess from the same cause, forming lower down, may cause symptoms related to the esophagus rather than the trachea. A similar condition may ensue in the course of a cervical Pott's disease, as also in the dorsal spine, in the latter condition giving rise to esophageal symptoms.

Peritonsillar abscess is rare in childhood, but its possibility must be borne in mind. It causes stridulous breathing but rarely symptoms which closely resemble obstruction. An extension of inflammation in this as in the preceding condition may cause edema of the glottis.

As already stated, dyspnea from enlarged thymus may under some circumstances be relieved by intubation. With this single exception none of the preceding conditions is alleviated by intubation, which is never actually, though often apparently, indicated. Tracheotomy, on the other hand, is frequently indicated to remove foreign bodies when an expert bronchoscopist is not available, and might be indicated in the last three conditions described.

Edema of the glottis and submucous laryngitis, though differing in pathology, present symptoms so closely akin that they are practically indistinguishable clinically. The epiglottis alone may be the seat of the edema, but more frequently the aryteno-epiglottic folds of the larynx are involved, and in some instances the process may extend into the trachea. The condition is caused by nephritis, or local irritation such as smoke or irritating gas, or in the course of arachidic bronchitis (Jackson), or as an extension from contiguous tissues such as peritonsillar or post-pharyngeal abscess, or erysipelas. It has also been observed in food idiosyncrasies such as egg albumin.

The symptomatology is usually sudden in its onset, and the patient is immediately in a desperate condition. Diagnosis is made by inspection, which may necessitate the mirror, and by digital examination, when edematous processes can be felt, frequently in the form of two soft bulging masses at the entrance of the larynx. Clinically, dyspnea is largely inspiratory. Frequently tracheotomy is necessary, but intubation is sometimes done successfully.

Papillomata of the larynx are occasionally met with in children. The first symptom is apt to be hoarseness, which may develop into a complete aphonia, while dyspnea, which is both inspiratory and expiratory, develops gradually, unless there is intercurrent catarrhal infection, in which case the swelling may be rapid enough to cause a sudden attack of dyspnea. When recognized early these growths may be removed from the larynx from above. If their removal is long delayed tracheotomy or laryngotomy may be necessitated. After the removal of such growths by the latter means a subsequent intubation is usually needed in order to prevent the closure of the air passages from postoperative swelling. The length of time the tube is worn depends entirely on the progress of the case.

Syphilitic Laryngitis.—Any portion of the larynx may become affected by syphilis, and any of its structures may be involved. The pathology may vary from catarrhal infiltration of the membrane, or the formation of granulomata, to ulceration of the cartilages. In most instances hoarseness is present; this is followed frequently by aphonia, and even stenosis. The latter is often indistinguishable clinically from a diphtheritic process. It is differentiated by inspection (mirror), bronchoscope, culture, or therapeutic tests. Intubation may become necessary.

Influenzal Croup.—A laryngeal stenosis of varying degrees of severity may occur in the course of an infection such as influenza, which especially attacks the mucous membranes. To this type of laryngitis Lynah has applied the name "Influenzal Croup." Several types are described, but for our purpose the laryngeal type and the tracheobronchial type only demand attention. These are differentiated largely by anatomical location and difference in onset and course. Either may produce stenosis. Each is indistinguishable from membranous croup except by means of the bronchoscope. Influenzal croup is apt to be more spasmodic and intermittent. In some instances the patient may apparently be in urgent need of intubation one moment and almost perfectly comfortable the next. There is not the same "gradual, progressive, rhythmic, inspiratory and expiratory dyspnea which is frequently present in diphtheritic croup." These symptoms are dependent for their appearance on a "tumefaction of the ventricular bands, which tend to close the glottic aperture." Sometimes there is a whoop from the same cause. The respiratory difficulty is largely expiratory. Intubation is sometimes indicated.

Spasmophilia.—To a physician who has not seen a child suffering from laryngospasm or laryngeal stridor, the attacks may cause confusion in diagnosis. The spasm sometimes completely arrests respiration. Intubation has been successfully employed for the relief of a prolonged, severe attack.

Bronchopneumonia when particularly severe has been mistaken for laryngeal stenosis, because of the rapid and apparently difficult breathing, especially when accompanied by cyanosis. A careful stethoscopic examination of the patient should render the diagnosis clear.

All of the preceding conditions may cause symptoms of laryngeal stenosis so severe as to be mistaken for membranous croup. I have seen in consultation each of these conditions when the diagnosis of membranous croup had been made by the attending physician. Some of these are fortunately of too rare occurrence to cause great difficulty in diagnosis. On the other hand, some may cause the greatest experts serious concern. The most serious mistakes, and those which more often cost the lives of patients, are made in connection with spasmodic croup and acute catarrhal laryngitis; not that they are often mistaken for membranous croup, but membranous croup is often mistaken for them.

Spasmodic croup is a condition of spasm of the larynx which is induced by or accompanies a catarrhal infiltration of the mucous membrane. It is common in children from the sixth month to the end of the third year, though in rare instances repeated attacks may persist into late childhood or even adult life. The congestion is more or less above the cords and is induced by exposure to dampness or high winds, or, in some children, by constipation or overeating, in which instance it would appear to take the place of a digestive upset. Well nourished and fat children are more prone to these attacks than are thin, emaciated ones; while some children are subject to frequently repeated attacks. There are several variations of type in this condition. In one there is hoarseness which commences late in the afternoon in a child that has appeared perfectly well during the day. This gradually increases until late at night when the characteristic high-pitched, ringing, metallic cough develops. This becomes severe and spasmodic, and is accompanied often by a deep, loud, inspiratory stridor which apparently "breaks" the spasm for a short while, only to return with renewed severity. The pulse is rapid, respiration slow, temperature but slightly elevated—if at all. The spasmodic stenosis may be so severe as to cause a pallor or even cyanosis. These symptoms become less and less severe until daybreak, when they usually pass off gradually, the child being quite well the next day. Another type presenting the same characteristics, except that the advent is quite sudden, often wakes the child about midnight out of a sound sleep, without any symptoms ushering in the abrupt onset. This type ends as suddenly as it begins. The third variation is that which does not clear up completely during the day, but leaves the child more or less hoarse between attacks; many of these are probably cases of acute catarrhal laryngitis. In spasmodic croup the voice is rarely lost completely. The attacks have a marked tendency to recur three successive nights with decreasing severity. The spasmodic character of the attacks, the clearing up during the day, and the absence of the loss of voice usually serve to distinguish this condition from diphtheritic croup. Not infrequently, however, the resemblance may be so close as to present a serious problem in diagnosis. In the event of the failure of the usual remedies for the relief of this condition, intubation may be necessary.

Acute catarrhal laryngitis though not so common, occurs with sufficient frequency to cause trouble in diagnosis. At times its severity is such that from clinical evidence alone it is impossible to distinguish it from an attack of membranous croup. There is hoarseness which, at times, may approach aphonia. The cough is of the "hacking" variety, and in the early stages is non-productive. It is usually mild during the day, but increases in severity at night, or there may be a steady increase in all symptoms to the point of marked stenosis with the accessory muscles of respiration being actively used. The constitutional symptoms vary from none at all to those of great severity, with high temperature and prostration. The dyspnea is inspiratory. There may be local symptoms of soreness in the larynx and trachea, or there may be severe pain. It is frequently difficult to distinguish between this condition and spasmodic croup, and when the symptoms are of sufficient severity to call for the use of an intubation tube it is quite impossible to distinguish it clinically from membranous croup. Inspection with the mirror, which is difficult in infants, or the bronchoscope, which is comparatively simple, are reliable. Culture, is of little value, because as is well known a positive culture in primary membranous croup is often difficult to secure.

Membranous Croup or Laryngeal Diphtheria

This is one of the most tragic situations known to medicine; its relief by intubation is as satisfactory as it is dramatic. Membranous croup may occur as a primary invasion of the larynx by the diphtheritic process, or secondary to a faucial infection, or as a simultaneous invasion. The primary type has no visible membrane in the faucial region; by laryngoscopic examination it may be readily seen in the larynx, but the use of mirrors in young children is difficult and often impossible. The bronchoscope in expert hands is a valuable and certain aid to diagnosis, but it is not always available, so it is largely by symptomatology and the clinical course that the diagnosis of this disease is to be made.

The onset is usually insidious, hoarseness, slight or severe, being the first noticeable symptom, and develops irrespective of the time of day or night. As the hoarseness increases the voice becomes more and more harsh or stridulous, and all symptoms gradually and steadily increase for from one to three days, the voice being gradually and completely lost. During this time the constitutional symptoms have been slight or entirely absent; in fact, the child has not even ceased to play. The temperature ranges from normal to rarely more than 101°. The pulse is generally rapid. The symptoms continue to increase until by the third day there is dyspnea which is slight at first but rapidly increases in its intensity until the accessory muscles of respiration are brought into action and labored respiration has taken the place of moderate dyspnea. The pulse becomes more rapid, while the respiration may be normal in rate, or even slower than normal. The alæ nasi dilate, the supra sternal and supra-clavicular spaces and the epigastrium retract and later the intercostal spaces also. The harsh, snoring, or sawing respiration of marked obstruction to *both inspiration and expiration* is now well established. The child looks anxious, the color becomes dusky. This rapidly gives way to cyanosis of lips and fingers first, and the cyanosis soon becomes general. The child is clammy with a cold perspiration, the struggle for air becomes intense; the cyanosis gives way to an ashy color, and the child dies of suffocation, sometimes in a terminal convulsion.

The temperature, which usually remains low during the early stages of the attack rises rapidly towards the end until it may reach 105 to 106°. The pulse also increases in rate and late in the attack rises rapidly as the respiration becomes more embarrassed. The mentality of the child remains clear until near the end, when stupor supervenes as the violence of the respiratory efforts reach the maximum. In the primary laryngeal type there is a signal absence of septic manifestations, nor is death in this type ever more than partially due to sepsis. The reason for this is that absorption of toxins from the larynx alone is slight, due largely to the poor lymphatic supply of this region. Death is due to suffocation alone in practically all cases.

Variations from this type are common. A child may develop a hoarseness so slight as to be barely noticeable, and may progress so rapidly through the stages already described that in the course of a few hours an intubation tube is urgently needed. This type differs from the preceeding only in the rapidity of the development of symptoms, and without the use of the laryngoscope may be indistinguishable from an influenzal croup. This type is most often seen in infants. On the other hand the condition may be so gradual in onset and the symptoms so slow in reaching a maximum intensity, that as long a time as ten days may elapse before it becomes serious enough to call for operative interference. In some instances the symptoms continue to be very mild, a laryngitis alone being suspected, when stenosis suddenly develops with marked dyspnea, and death occurs from suffocation before the aid of an intubator can be evoked. All of the classical constitutional symptoms which accompany faucial infection may be, and usually are entirely absent in cases of primary involvement of the larynx. Secondary involvement in the course of, or following a primary faucial infection, presents a vastly different picture. All of the symptoms of laryngeal stenosis are added to those of the recognized syndrome of a faucial infection. In neglected cases of faucial diphtheria the sepsis may be extreme; the massed cervical adenitis alone can cause very serious embarassment either from direct pressure or complicating edema; when this is added to the membranous laryngitis, the condition becomes one of the most desperate and critical known to medicine. Secondary cases may develop after the subsidance of a supposed follicular tonsillitis. The descriptions as outlined are, of course, those of untreated cases.

Diagnosis.—The salient points in the diagnosis have already been discussed under the description of the several conditions causing laryngeal stenosis. The actual diagnosis may be very briefly stated as follows—a croup which comes on during the day and steadily increases or one which sets in at night and does not tend to clear up in the day can safely be considered of diphtheritic origin. In other words, "diphtheritic inflammation may be assumed if there is severe, constant and increasing dyspnea with aphonia."

In a considerable number of cases of membranous croup the parents think the child merely has a severe cold, and employ "home remedies" until the dyspnea is so severe that when a physician is called the child is saved with great difficulty, if at all. This is especially apt to be the case when the child is accustomed to having catarrhal croup. On the other hand, stenosis is common after an attack of what has been diagnosed as follicular tonsillitis.

Dependence should never be placed on bacteriological examination alone, because when first seen many of these cases are in urgent need of a tube, and its introduction should not be delayed by attempts to secure a culture. Smears from the larynx are difficult to secure, and even in the presence of a visible membrane are often negative. The bronchoscope furnishes positive evidence, but it is not always available, and at times the delay incident to this procedure would be dangerous to the patient. Hence, clinical diagnosis alone should be relied on, outside of specially equipped centers.

Incidence.—The greatest number of cases of laryngeal diphtheria are seen between the first and fourth year. Under one year it is rare, though even nursing infants are sometimes affected. (The youngest patient I have ever intubated was one of two months.) The number of cases of membranous croup seems to bear no definite relation to the number of cases of diphtheria in the community at the time. A relatively large number of cases of croup may occur when there is very little diphtheria in the community. On the other hand, a number of cases approaching epidemic proportions may exist without a single case of laryngeal involvement. In the experience of the author the incidence is greater from January 1 to April 1, though this may differ widely in different parts of the country and with different years in the same community.

Prognosis.—The outcome of a case of laryngeal diphtheria is dependent on so many factors that a positive statement is quite difficult to make. Before the days of antitoxin, and especially before the advent of the intubation tube (even with the aid of tracheotomy) the mortality was appallingly high. A child suffering from primary laryngeal involvement, over one year of age, to whom antitoxin is administered early and an intubation performed in ample time can almost always be saved. Infants under a year withstand diphtheria badly, and the strain of the stenosis can be endured for only a very short period. Then, too, however skilfully an intubation may be performed there is a shock to the young infant which is rarely observed in older children.

Bronchopneumonia is more apt to develop as a complication in infancy. Under the best possible circumstances, laryngeal diphtheria is a very serious condition during infancy. The intercurrence of pneumonia is not due to the diphtheria nor to the fact that intubation has been performed, but is merely a complication such as may occur in any other serious and depleting illness.

In secondary involvement, toxemia, which is far more marked in pharyngeal than in uncomplicated laryngeal cases, is added to the strain of stenosis. Moreover, we must never lose sight of the fact that mixed infections with other organisms are exceedingly common and add to the gravity of the situation. They may be assumed to exist when there is much glandular involvement. Bronchopneumonia makes the situation extremely grave. Most cases of diphtheria die from this complication or as a result of cardiac failure. The latter is especially common in laryngeal involvement. This is not surprising when we recall the fact that the dyspnea of stenosis puts a severe strain on an organ whose muscles are already affected by a toxin which has a special predilection for this type of muscle.

In general then, the prognosis depends largely on whether a case is one of primary or secondary infection; on how long the illness has existed before the diagnosis; on how long a stenosis of appreciable severity has existed; on the condition of the heart; on whether a sufficiently large dose of antitoxin has been administered, and how early; on whether an intubation has been performed early or late; on whether the intubation was performed in an expeditious and expert manner, or whether many attempts were made by an inexperienced hand; on the general management of the case, particularly the after care, if intubation has been performed.

Treatment.—The treatment of laryngeal diphtheria may be summed up in a few brief statements: The administration of an adequate dose of antitoxin as soon as the diagnosis is made; intubation as soon as the first symptoms of stenosis are manifested; and absolute quiet for the patient. Wide variation of opinion exists in different sections of the country as to what may be considered an adequate dose of antitoxin. A safe range is from a minimum dose of 5000 units to a maximum of 20,000 units. A mild uncomplicated case of laryngeal involvement in which the stenosis is slight or absent, in a child of one to two years may need only 5000 units, if an early diagnosis is made. A severe case of both laryngeal and faucial involvement will require 20,000 units. Between these two extremes the size of the dose must depend on the severity of the case, age of the patient, and the day of the disease. It must be remembered that in uncomplicated laryngeal cases the septic manifestations are secondary in importance to the obstruction. It must be remembered also that antitoxin neutralizes only a small portion (10 to 20 per cent.) of the toxins already in the system, but prevents the formation of any additional toxins and that when given hypodermically takes from 9 to 24 hours to show definite effects. It is preferable therefore to administer the dose intramuscularly, deep into the gluteus, or in severe cases intravenously. A very small dose of antitoxin given by the venous route is far more potent than many times the amount administered by any other route. *A sufficiently large dose should be administered at one time rather than* *repeated doses. When there is the slightest doubt as to the diagnosis, antitoxin should be administered, since a life may thereby be saved, and it does no harm if the case is not diphtheria.*

Intubation.—The next step in the treatment is the introduction of the intubation tube. When the case is seen for the first time and the tube is needed urgently, it should be introduced at once and the antitoxin administered afterwards. By far the larger number of cases come to the operator for intubation late in the course of the disease—many of them so late that it is with difficulty they are saved at all. Many are not saved because of needless delay in intubating. When the suprasternal and epigastric spaces begin to retract, showing that the stenosis is of sufficient severity to necessitate the aid of the accessory muscles of respiration, and the pulse is increasing in rapidity, intubation should be performed without delay. When the intercostal spaces are retracting with inspiration the child is in imminent danger, and when there is cyanosis the case is desperate indeed. The longer the stenosis lasts without relief, and the more rapid and thready the pulse becomes, the more hazardous the convalescent period, with death resulting in many cases after the stenosis has been relieved by a tube. Too much emphasis cannot be placed on the fact already referred to that the strain on the heart from labored respiration is very great, thus weakening an organ for whose muscular framework diphtheritic poison shows a special predilection. It is far better to perform intubation early—even unnecessarily—than to wait too long. It is almost conservative to say that an intubation cannot be performed too early.

Occasionally the difficulty encountered in distinguishing laryngeal diphtheria from laryngitis and tracheitis from other causes, especially influenza, makes it advisable to use a laryngoscope for diagnostic purposes. It is frequently the case, however, that an expert intubator is available while one accustomed to the laryngoscope may not be. Consequently, it is wiser to intubate when in doubt. In cases of laryngeal diphtheria which have been neglected it is comparatively easy to remove the membrane by means of forceps through a bronchoscope or even a laryngoscope. The membrane can also be removed by means of gauze grasped in the jaws of the forceps or applicator in such a way as to pass through the membrane folded down like an umbrella, so that on withdrawal it opens in a manner similar to the old esophageal probang and wipes the membrane out. Such a procedure as this, however, must be attempted only by one who is an expert intubator, laryngologist, and tracheotomist.

Recently, membrane which has begun to separate has been removed by suction apparatus introduced through the laryngeal endoscope.

The systemic treatment consists almost exclusively of rest which must be rigidly enforced. If the child is docile, the recumbent posture is not difficult to maintain. The child should not be allowed to rise in bed for any purpose even though it becomes necessary to apply a binding sheet. When there is much sepsis, or restlessness, or the heart is either rapid and thready or abnormally slow, showing myocardial involvement or impairment of the innervation of the heart, morphine is the "sheet anchor." This is the only drug needed and should be employed without hesitation as often as needed. Alcohol, caffeine, and camphor are used as cardiac stimulants by some, but it is doubtful if they really do good. Digitalis is positively contra-indicated. Inhalations of medicinal vapors or steam are of no avail, and emetics should not be used because of their depressing action on the heart.

The feeding of older children during the period of the tube is rarely difficult; soft and semi-solid foods are taken with ease, even liquids seldom giving any trouble. In young children there is often much inconvenience from the dropping of milk and water into the lumen of the tube, causing annoying cough, which may result in a forcible expulsion of the tube before the proper time. This can usually be avoided by lowering the child's head while feeding so that it will be below the level of the shoulders. This is not difficult with either the breast or the bottle feeding. In some instances, particularly in young infants, the swallowing with the intubation tube in place causes such discomfort that the child will not take a sufficient amount of food. In such cases one must resort to the stomach tube, the tube being passed either directly through the pharynx into the esophagus or through the nose. The necessity for stomach feeding rarely lasts more than a day or two.

The length of time the tube remains in the larynx depends on circumstances. A safe average time is five days. As a general rule, a tube removed at this time does not have to be replaced. Not infrequently a tube is coughed up before this time, and the child may not need re-intubation. On the other hand, if the tube is removed at what may appear to be the proper time, it sometimes has to be replaced at once.

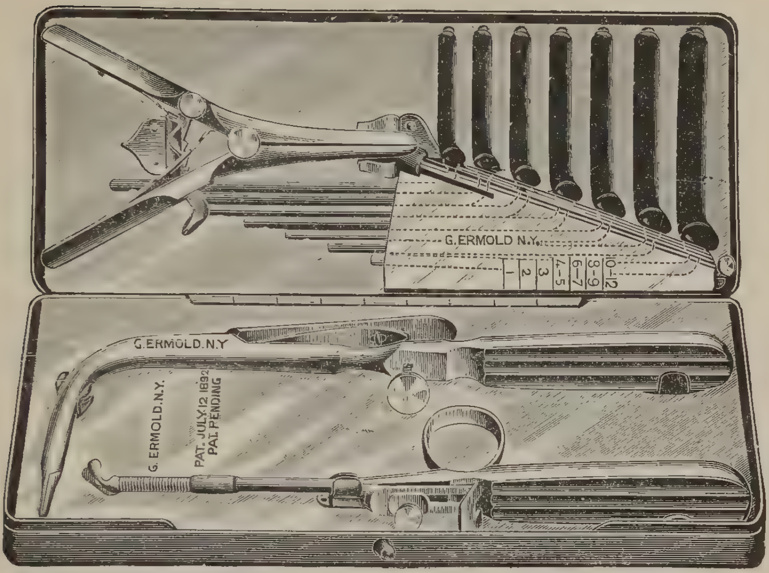
Caution is often advised against allowing a child to lie on its side or face while wearing an intubation tube, because of the supposition that in such position the tube may be expelled more readily by coughing. This danger is much exaggerated for the child may with impunity be allowed to assume the position which is most comfortable, so long as it is recumbent.

The Instruments.—The world of medicine and mankind at large owes no greater debt of gratitude to the genius of one man than to that of Joseph O'Dwyer, the designer of the intubation tube. With untiring energy and a perseverance which eventually overcame all obstacles, making success out of what had hitherto been failure—an effort to relieve the mechanical obstruction caused by diphtheritic membrane in the larynx—he perfected the intubation tube which bears his name. To do this, many hours of the day and by candle light at night in the morgue he studied the larynges of those dead of the disease, and took casts and made models from them until he produced a perfect instrument. Many "improvements" on his instruments have been attempted, but on inquiry it will be found that all of these had been tried by him and abandoned. There is but one perfectly adapted set of instruments for the purpose, and that is the O'Dwyer set.

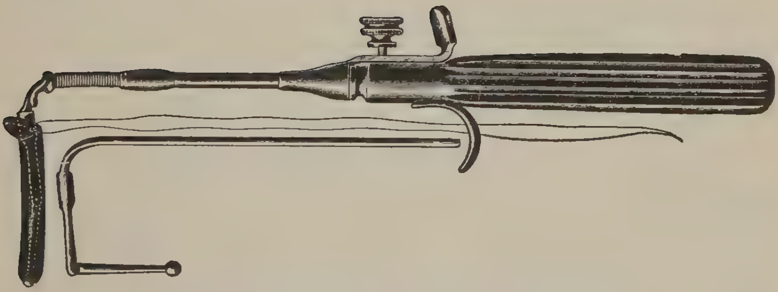
The instruments required for the operation consist of tubes of lengths and diameters which vary with the ages of the patients: An obturator, extubator, gag, and scale. Eight tubes are used varying from the smallest—for a six months old infant—to the largest for a 12 year old child. Adult sizes are also made. The tubes are so designed that a large flange or head (through which is a hole for the thread of silk) fits into the glottic aperture, thus preventing the entrance of the tube further into the larynx, and a swell or "belly" about midway which slips between the vocal cords and prevents the tube from being coughed up, it being retained by the swell below the cords. When the tube is in place the epiglottis fits snugly over the aperture in a normal manner. The first tubes which were made were of lead alloy plated with gold, and the lumen lined with the same metal. These were afterwards abandoned for hard rubber, the lumen being lined with gold plated metal cylinders. Solid aluminum has also been used, but with the exception of a few who still prefer the gold tubes, those of hard rubber are in general use. Those who prefer the gold tubes do so because the weight is supposed to prevent their being easily coughed up. This is a negligible advantage, and as a matter of fact they are coughed up just as frequently as the rubber tubes. The objection to metal tubes is that a calcareous deposit forms on them from the secretions, and they become rough and scrape the mucous membrane during removal. In addition to the regular shaped tubes for general use there are several varieties, built on the same plan but with the expanded portions in somewhat different places (Lynah) for the purpose of better retention, and also others with specially "built up" heads. These are all known as retention tubes.

The introducer consists of a curved instrument with an "obturator" which fits into the lumen of the tube while introducing. The obturator is hinged to facilitate its withdrawal, and the instrument is equipped with a thumb spring attached to a rod which is forked at the end for the purpose of pushing the tube off the obturator. The extubator is curved as is the introducer, and is equipped with expanding jaws (resembling a duck bill) which fit into the mouth of the tube. Pressure of the thumb opens the jaws within the tube and holds it during withdrawal. The gag is of course used to hold the jaws apart during operation and the gauge is for the purpose of determining the size of the tube to be used, the measure being made by "age length."

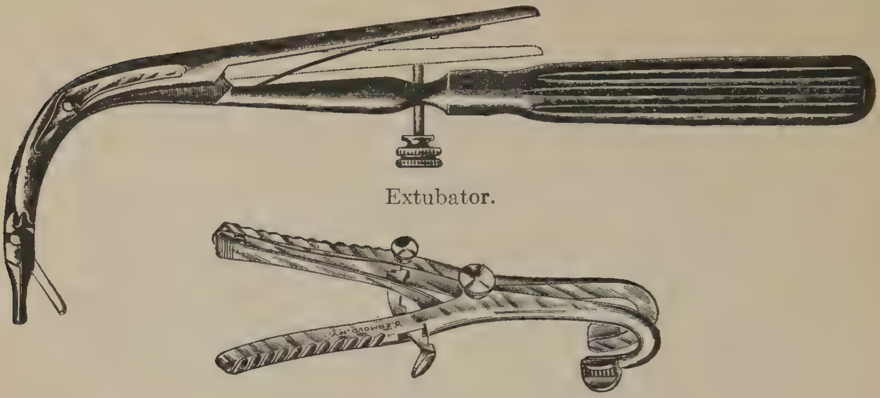
Direct intubation is performed through an electrically lighted bivalve speculum which is introduced in the mouth as far as the glottic aperture and then opened and held thus by means of a set screw. The position of the child for this procedure is recumbent, the head being held in extreme extension. The introducer and extubator are the same instrument, which consist of a long forcep whose jaws are identical with the extubator of the O'Dwyer set. The operator



O'Dwyer intubation set.

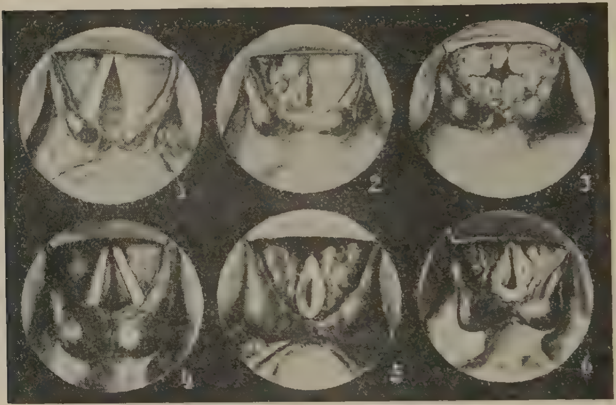


Introducer and obturator with tube in position.

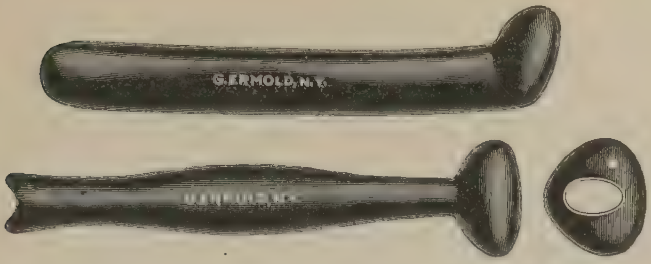


Extubator.

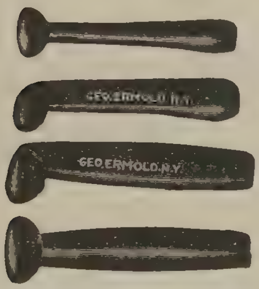
Gag.



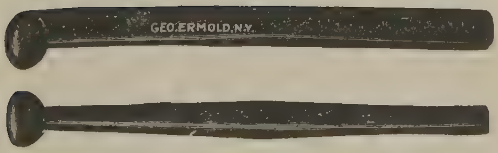
These are photographic reproductions of water colored drawings taken from life. From left to right the top row shows: 1. Normal larynx. Note the speculum blade at the top of each of the pictures. 2. Larynx in acute diphtheria. Note the entire cavity of the larynx is filled with membrane. The ventricular bands and vocal cords are completely covered, and there is very little space between the cords for respiration. There is marked swelling of the aryepiglottic folds and arytenoid cartilages. The child was intubated for two weeks and made a complete recovery. 3. The larynx in a child one and one-half years of age. The larynx was completely filled with membrane and there was extension into the trachea and right bronchus. The entire membrane was removed by direct laryngoscopy and bronchoscopy. The child was then intubated with a long tube. The patient succumbed two weeks later to diphtheritic bronchopneumonia. 4. Direct picture of the larynx in a boy of six years. Marked subglottic edema below the vocal cords. The boy suffered with both inspiratory and expiratory dyspnea but the voice was practically normal. Note the enormous tumefaction of the arytenoid cartilages. The boy was not intubated and made a complete recovery after a large dose of antitoxin. 5. The acute diphtheritic larynx in a girl of 10 years. The membrane was confined to the vocal cords and ventricular bands and did not extend beyond this area. Intubation was necessary, the tube being worn for four days. She made a complete recovery. 6. Shows a similar condition of the larynx in a girl of 11 years. The membrane has extended well out into the cavity of the larynx. There was no extension downward. The child was intubated, but made a perfect recovery. The diphtheritic exudate was primary in the larynx and showed no sign of extension into the trachea and bronchi except in the very young child recorded as picture 3. (H. L. Lynah in N. Y. Med. Jour.)



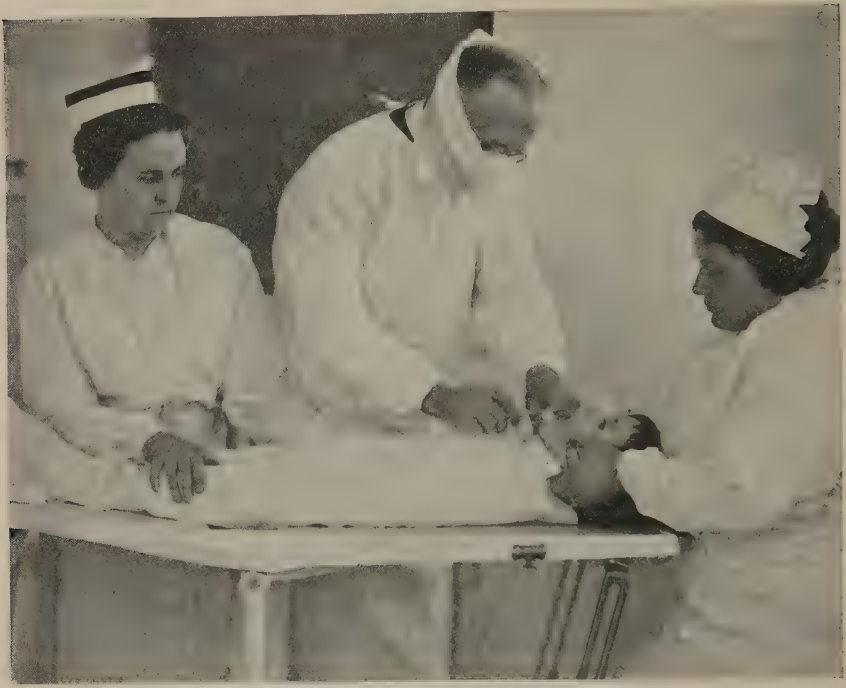
Regular intubation tubes, lateral and anteroposterior views.



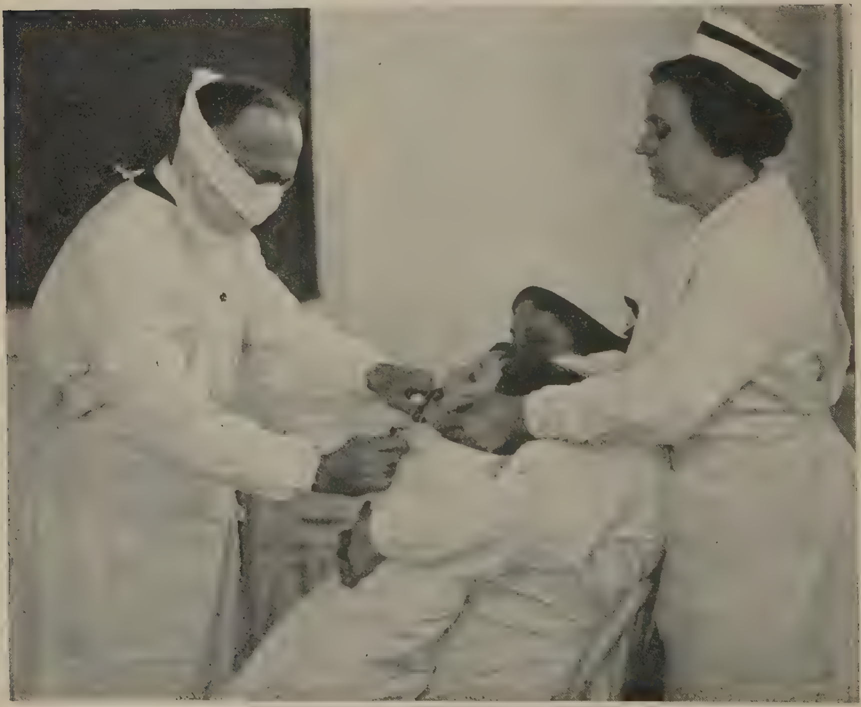
Special retention tubes.



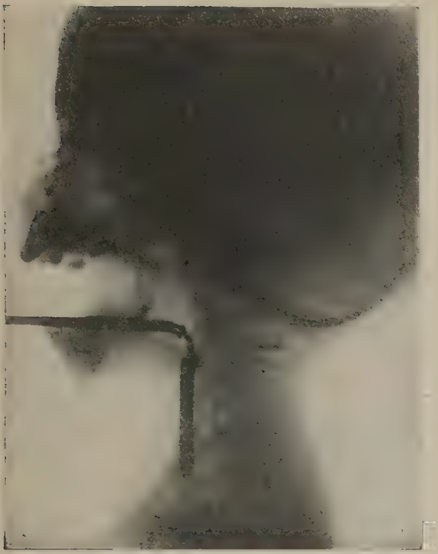
Lynah tracheal tubes.



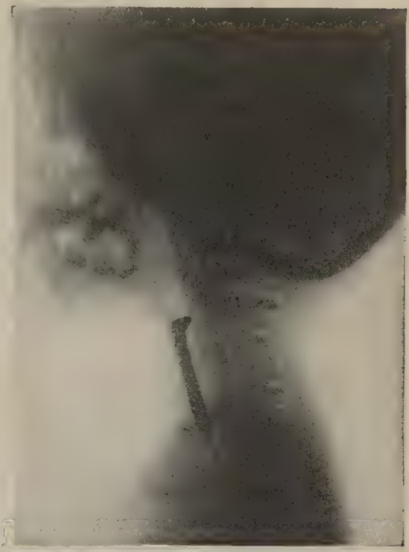
Recumbent position for intubation.



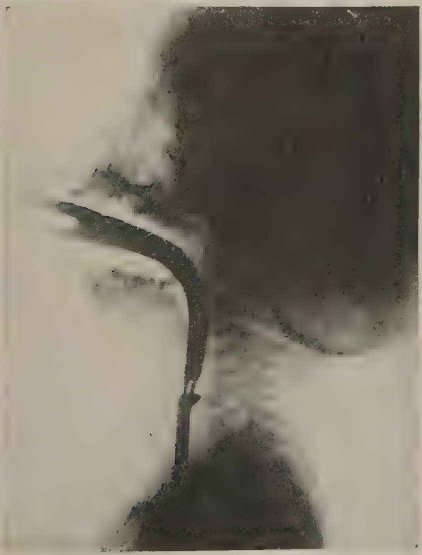
Sitting position for intubation.



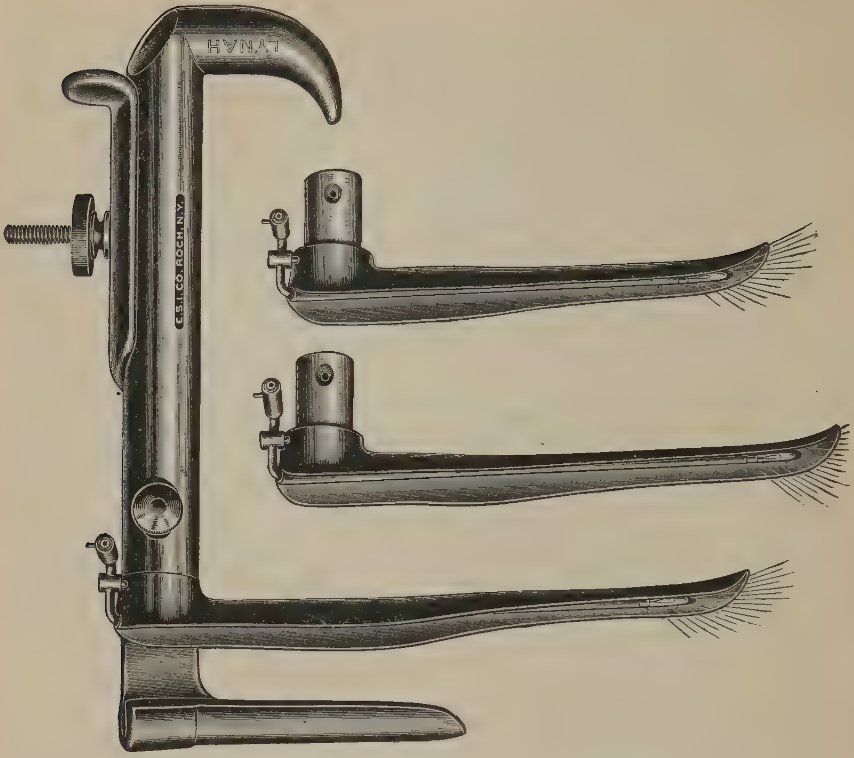
Roentgenogram of introduction of tube.



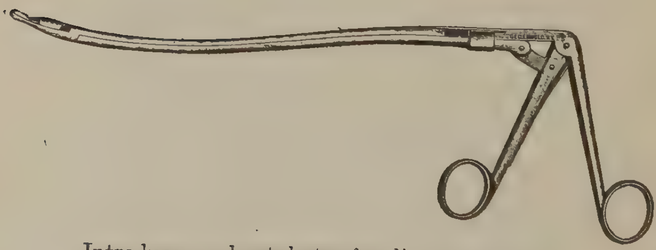
Roentgenogram of tube in larynx.



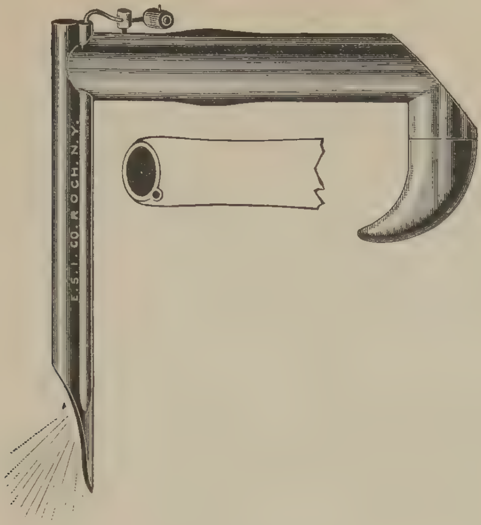
Roentgenogram of extubation.



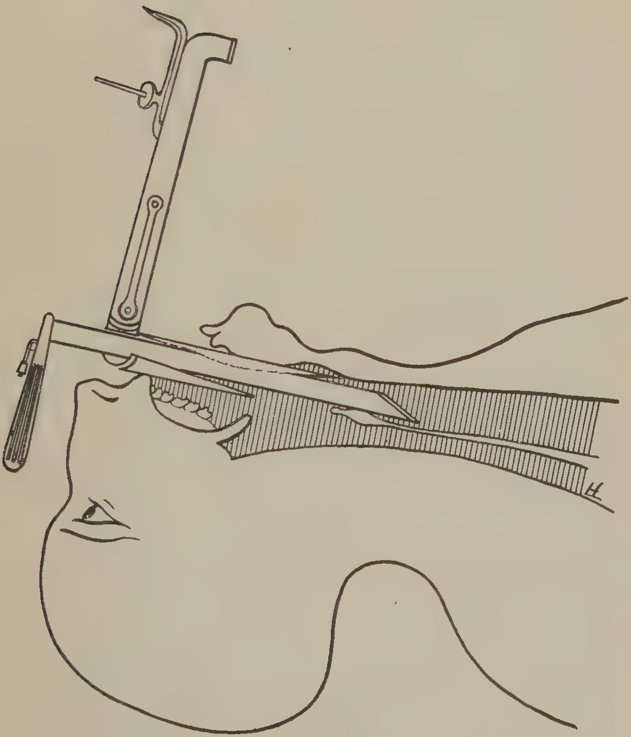
Lynah bivalve speculum used in direct intubation.



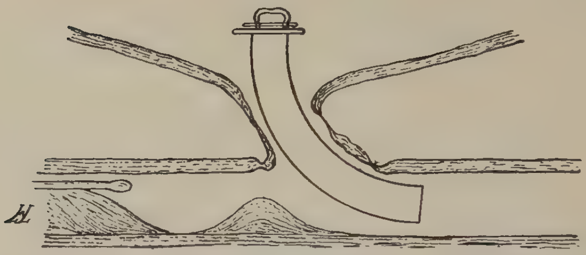
Introducer and extubator for direct operation.



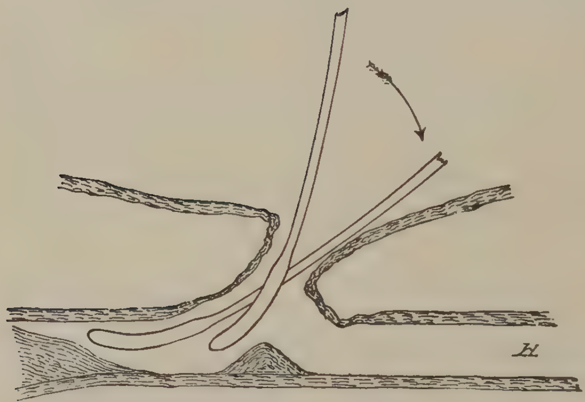
Tracheoscope.



Tracheoscope in position (diagrammatic).



Bouginage of laryngeal stricture, above tracheotomy tube (diagrammatic).



Bouginage of laryngeal stricture through tracheotomy wound (diagrammatic).

sits on a stool at the head of the table and introduces the tube into the larynx by direct inspection. Direct intubation requires a very much longer time to perform than does indirect, and is hardly practical outside of well-equipped hospitals.

Introduction of the Tube.—Intubation is one of the most delicate procedures known to medicine, and requires the utmost skill and dexterity to secure the best results. To one who is well trained, it becomes quite easy. One who has not been well trained under a competent instructor should not attempt it. Prolonged practice on the cadaver under expert supervision is absolutely necessary before an attempt is made to intubate a living child. Dr. O'Dwyer always insisted on this type of training.

Two positions are used while inserting the tube. One is the upright posture in which the child is held in the lap of an assistant, or with its legs between the assistant's knees. The head is so placed as to rest on the assistant's *left* shoulder and held firmly and somewhat extended by a second assistant who also holds the gag so as to prevent its slipping. In the second position (the one preferred by most intubators) the child is placed on its back on a table, an assistant sits or stands at the head, with the child's head near the edge of the table. In this position the attendant holds the head firmly and retracted by a hand spread out on each side of the head.

A prerequisite to the best work is that the child be secured by means of a winding sheet, wrapped from the shoulders to and including the feet. Usually three safety pins are used, one to secure the sheet snugly at the shoulders, the arms having been previously placed alongside the body, the second at the level of the hips; and a third secures the sheet at the ankles. In this manner alone can the child be held securely enough to justify an attempt to introduce the tube. In the second position the knees may be held by an assistant or by the knee of the operator, if a second assistant is not available. The child need not be held at all if he has been properly wrapped. In an emergency, if the operator is an expert, it is possible to accomplish the intubation though there is no one to hold even the head.

The gag is inserted in the *left* side of the mouth (operator's right) to be out of the way of the left hand of the operator, opened as far as possible, and is held in place and prevented from slipping by the assistant with the thumb of her left hand, pressing backward against the screw which holds the blades of the gag together. This is done while the hands are holding the head. The operator stands at the left of the table (patient's right) or in front of the patient if in the upright position. The forefinger of the left hand is inserted into the pharynx at the base of the tongue until the epiglottis is felt. The epiglottis is then lifted and held between the ball of the forefinger and the base of the tongue. In this position the cricoid cartilages may be felt. The finger is shifted slightly to the left (patient's right) until it rests on the right cricoid cartilage. The introducer with tube in place, which has previously been made ready, with string attached which is wrapped around the little finger of the operator, is passed in the midline of the mouth and along the outer (inner, in relation to the patient) palmar border of the guiding finger in a backward and downward curve (anatomical position) and passes directly into the larynx, until the head of the tube is beneath the tip of the finger. The thumb-spring rod of the introducer is then pressed to release the tube from the obturator by means of the forked end, and with the guiding finger of the left hand holding the head of the tube, the introducer is quickly withdrawn in reverse order, the hinge in the obturator facilitating the curving motion or withdrawal. The guiding finger is withdrawn from the mouth and the gag removed at once, and the intubation is accomplished. Many intubators do not need the releasing instrument at all.

From the time the gag is in place to the withdrawal aftei intubation should require about ten seconds, if the operator is experienced. Rapidity and dexterity are required in this work since at the time of introduction, while the obturator is still in the tube, there is a short space during which the passage of all air is interrupted. Quickness is also required to cause the least amount of shock. Rarely more than one attempt is needed at introduction, although, an expert may make repeated short efforts with far less shock then would be caused by an inexperienced operator.

As soon as the obturator is withdrawn there is a hissing, rattling sound which demonstrates that the tube is in the larynx, and that there is free passage of air. When this sound does not occur we may be sure that the larynx has not been entered. This proof should not be necessary, however, for the experienced operator *knows* whether or not the tube is in the larynx before withdrawing the obturator.

The tube is selected by ascertaining the age of the child, and measuring the tube with the gauge belonging to the set of instruments. In deciding on the size of the tube it is well to take the next coming birthday of the child as a guide if the child is large and well developed, and the last birthday if the child is small for its age. This is important since a tube which is too small may be coughed up immediately, and one that is too large may stretch the larynx causing irreparable damage. It is wiser, however, to use a tube which is too small than to stretch the larynx with one which is too large.

After the operation there is a period of coughing from irritation of a foreign body, and until this is over the silk cord is usually left in position. To remove the cord, one end is cut near the lips, the forefinger of the left hand is passed quickly into the larynx (with or without the use of the gag) the epiglottis lifted, the finger held on the head of the tube and the string is withdrawn. This usually requires about two seconds.

After a little while, depending on the amount of obstruction and the time it has existed, the child drops off into a profound sleep for a number of hours, during which the pulse comes down rapidly, unless the myocardium is badly damaged. There is usually a reactionary rise in temperature closely following the intubation. It is difficult to say just how much this is due to the operation alone and how much is due to the antitoxin which is often administered about the same time the tube is introduced. The temperature declines gradually and is usually normal by the fourth or fifth day, and this is a fair guide to the indication for the removal of the tube.

Extubation.—This is more difficult than intubation, and the difficulty increases in proportion to the youth of the patient. In the case of a child of six months it is often extremely hard to do.

Extubation is performed in a similar manner to intubation, the preparation of the patient being identical. The extubator is inserted into the pharynx with the index finger of the left hand as a guide and with great dexterity and infinite gentleness is inserted into the lumen of the tube. When certain that this is in place the thumb is pressed on the upper blade of the instrument, and jaws which enter the tube closed, are opened and held open, thus exerting their pressure from within, and the tube is withdrawn with an upward and forward motion (anatomical position).

Preparation and Care of the Tube.—Before intubating, everything should be in readiness to the minutest detail. The proper size of tube having been selected, a paraffined silk cord (that used by dentists is excellent) is threaded through the opening for that purpose, in the head of the tube and the two ends knotted. The cord should be long enough to be held tightly by the little finger of the right hand while intubating. This is of course for the purpose of retaining control of the tube in the event it is placed by mistake in the esophagus instead of the larynx. It is well to see that the various bearing parts of the intubator, obturator, and extubator are well lubricated and that the lumen of the tube is perfectly clean. When the instruments are not used for a long time the whole set should be gone over periodically to see that everything is in perfect order in the event of an emergency. Metal tubes may of course be boiled, but the hard rubber ones are distorted and cracked by repeated boiling, and in addition, the rubber is apt to separate from the lining. A good cleaning with soap and water using a pipe cleaner for the lumen, followed by a soaking in alcohol or bathing spirits is sufficient cleansing.

Accidents, Complications, and Sequelæ.—The introduction of the tube into the esophagus is the most natural and harmless accident which can occur in the course of intubation. There is no particular danger attached to this, since the tube has often been swallowed by the patient, both while an attempt at intubation was being made, and from coughing up the tube. It eventually passes with the bowel movements without inconvenience. The accident is to be avoided, however, because of needless delay in giving relief to the patient, and also the necessary shock it may cause through vomiting. It should be prevented while intubating by the silk cord, held by the little finger as already described.

An inexperienced operator may insert the tube into one of the ventricles of the larynx and force it through the laryngeal structures into the cellular tissues. This accident can be avoided by keeping the introducer and tube exactly in the mid-line of the body, that is, in the sagittal plane, and by avoiding force in the introduction. The accident can be at once recognized, by the fact that there is no relief of dyspnea and that the tube does not descend into the larynx low enough for its head to be below the epiglottis. The tube should slide promptly and easily into the proper position.

When intubation is performed late in the disease the membrane may become loosened during the operation. Strips of membrane and much mucus are often expelled by the first efforts at coughing. This loosening of membrane constitutes a real danger, since during the coughing efforts loose pieces of membrane may be forced into the tube, thus obliterating the lumen and inhibiting the passage of air; or the membrane may become loose at one point and remain attached at another and form a flap or trapdoor and impede respiration by blocking expiration only. In the event of such an accident (which is quite rare) the tube is removed at once by means of the cord which is still attached, and after a few minutes replaced. The removal of the tube under such conditions is often followed by the forcible expulsion of loose membrane, and not infrequently the symptoms of stenosis are relieved, and the tube does not have to be replaced.

Also, if the tube becomes blocked, a forcible cough may expel it, and it may have to be replaced at once, or, if the symptoms are relieved it may not be necessary to replace it.

If extubation is attempted carelessly or by an inexperienced hand there is possibility of the tube being pushed farther into the larynx. This is unusual, but I have seen instances of it. If care is not taken to set the extubator to fit the mouth of the tube or, if a wrongly made extubator is used, there is danger of introducing the extubator between the larynx and the tube, thereby splitting the larynx.

When a tube of the right size is employed everything proceeds smoothly, but if the intubation has been performed late in the course of the disease the child may continually cough up the tube—or even the next size larger, if this is tried. Undoubtedly this is due to paralysis of the laryngeal muscles, and rarely occurs if intubation is done early in the course of the disease. If too small a tube has been employed it is usually coughed up in the course of a few minutes to a few hours, and has to be replaced promptly. After this is done a few times and the child shows it can not do without a tube it is wise to insert the next size tube. This usually relieves the condition, but, unfortunately, the solution is not always so simple. Occasionally under these circumstances, and also when the tube has been removed intentionally at what seems to be the right time, the child appears all right for varying lengths of time from a few hours to a few days, when symptoms of stenosis gradually begin to recur and a reintubation is needed. Sometimes instead of the symptoms recurring gradually, the child appears quite comfortable when suddenly it develops an attack of stenosis with cyanosis, and intubation must be performed with great speed. This condition may continue for weeks or months and constitutes a serious complication. The cause of it has been the subject of much discussion and various theories have been advanced. In those cases which cough up the tube repeatedly even when a large tube has been employed there most likely exists a paralysis of the laryngeal muscles. It is doubtful whether this can be the cause when the tube is retained but can not be dispensed with as in the cases of recurrent stenosis. In some cases it is likely that granulation tissue from an ulceration at the site of diphtheritic membrane implantation may take place. The existence of this has been denied by many observers, but when intubation and extubation even in expert hands is followed by bleeding, it may be assumed. In other instances it is most probably due to recurring attacks of edema which come on in the sensitive mucous membrane whenever the pressure of the tube is removed. Various procedures have been advocated for the treatment of these conditions. The coating of the tube with gelatin impregnated with an astringent such as alum, has been tried, but it is doubtful if it does any good. The gradual stretching of the larynx by the use of larger tubes may be tried, the increase in size being at least one week apart. This too, is seldom of benefit. After all the other measures have failed, tracheotomy must be resorted to. Fortunately the number of such cases is small.

A child's inability to dispense with a tube is not infrequently of neurotic origin. Occasionally children become so much terrified when the tube is removed that they work themselves up into a state of excitement that necessitates reintubation. Some of these children resist extubation strenuously because of this nervous dread of needing the tube. This is not alone in older children, but infrequently occurs in the very young. Proof of this is to be found in the fact that if these children are extubated under anesthetic, the tube does not have to be replaced, also where the tube is expelled by coughing and the child does not know it, it does not need replacing. Some of these cases can be managed by administering an opiate a short while before performing the extubation, so that the child will be partially or completely asleep at the time of the operation.

Ulceration of the larynx occurs in a definite percentage of all intubations at the lower end of the tube, but rarely causes any serious trouble. An ulceration may, however, be deep enough to affect the cartilages of the larynx or the tracheal rings, causing cicatricial stenosis. Obviously this constitutes a most serious complication. It is more apt to occur in cases of edema from irritant inhalations than from diphtheria. Only one such instance has come under my notice, and that followed suffocation from smoke. The cicatricial contraction may be kept open for a long while by repeated intubation, but eventually tracheotomy must be performed. When this condition is recognized it is wiser to perform the tracheotomy early and institute special treatment looking to dilatation at once.

The methods of treatment introduced by Lynah, and in general use in hospital practice, have accomplished a great deal in permanently relieving all of those conditions described as complications. It is in this field of after treatment that his work is most useful. By use of the retention tube with the swell at the lower end rather than in the middle, many cases of prolonged intubation can be relieved. These tubes are introduced in cases of granulation and paralysis, and may do temporary or, even occasionally, permanent good in cases of cicatricial stenosis. It is in this last class of cases that laryngoscopy and treatment by direct inspection has found its greatest field of usefulness. When the fact of cicatricial stenosis is established it is best to perform the tracheotomy at once, and begin gradual dilatation of the larynx with olive tip bougies. These are used in two ways depending on the location and the degree of stenosis. In some instances it is well to dilate through the laryngoscope from above; in other instances the tracheotomy canula is removed and dilatation performed through this opening. This treatment is slow and prolonged, but results amply justify the time and perseverance required. Such treatment relegates to a past period the older picture which we recall when the tracheotomy cannula was worn indefinitely, the patient usually dying from an intercurrent pneumonia.

Tracheotomy.—This operation for the relief of laryngeal stenosis in membranous croup has been abandoned as first choice, intubation having entirely supplanted it. The advantages of intubation over tracheotomy are quite apparent to one who has seen cases treated by both methods. Tracheotomy is a cutting operation, with much attendant shock; it takes longer to perform; it leaves an open wound, which almost invariably becomes infected, with the result that the patient has an additional septic condition implanted on the first one. Bronchopneumonia is a frequent—almost invariable—complication in primary tracheotomies, and cicatricial stenosis often follows the operation. Most of these objections are absent with the use of the intubation tube. The only argument in favor of tracheotomy is that the tube is not expelled by coughing as readily as the intubation tube and that if it becomes stopped up, the inside canula of the tracheotomy tube can be removed and cleansed by one who is not trained, while this accident occurring with an intubation tube requires the immediate attention of a skilled person. The accident is fortunately rare, and when it does occur, an intubation tube is more than apt to be expelled by coughing. It is often argued for tracheotomy that the membrane may be implanted so low that the intubation tube does not reach it. This is sometimes true, but in such instances neither will a tracheotomy tube reach it. For these cases Lynah has devised a modified O'Dwyer tube which is long enough to reach the full length of the trachea. It of course must be introduced by the direct method. It is doubtful if even these would often relieve such a situation, since where the membrane extends to the bifurcation of the trachea it also often extends into the bronchi as well. These cases constitute diphtheritic bronchitis and the membrane often extends deep enough into the bronchial tree to justify the diagnostic terminology "diphtheritic pneumonia."

Occasionally, a membranous cast of the bronchial tree and even deeper structures is coughed up.

There are certain conditions causing stenosis of the larynx or trachea which are relieved by tracheotomy, and these have been discussed early in this article and the indications for operation pointed out. The indications for the employment of tracheotomy have also been discussed. Whenever possible intubation should be performed in a hospital, or at least the patient should be removed to one as soon as the tube is inserted, if the case is of sufficient urgency to require intubation when first seen. Very few nurses have had the training which enables them to properly care for these cases, and those who have, are usually in contagious disease hospitals, or in those having departments for contagious diseases. When this cannot be done, especially in small towns and country districts, one should not hesitate to perform the operation, since excellent results can be obtained in very poor surroundings. Some of my best work has been done many miles away from the city in remote country places. The cord should be removed from the tube after the child is quiet when the case can be reached quickly by the physician. Whenever the location is inaccessible, it may be advisable to leave the cord attached and fastened by means of adhesive plaster stuck to the cheek. When this is done the child should remain in the winding sheet.

Fortunately, all of the complications and sequelæ mentioned are exceedingly rare in comparison with the large number of intubations performed, and should never be taken into consideration when the operation is needed. I have had one series of 100 consecutive intubations without a death, complications, or sequelæ of really serious moment. Undoubtedly in the vast majority of instances both complications and sequelæ result from two causes: Too long deferred intubation, and incompetency.

Every community, however small, should have at least one physician who is capable of performing intubation; in this way many lives can be saved which are otherwise sacrificed.

CHAPTER CXLIII

WHOOPING-COUGH

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Definition.—Whooping-cough is a specific infectious disease characterized by recurring attacks of spasmodic cough, each paroxysm ending with a peculiar crowing inspiratory whoop and the expulsion of mucus from the upper respiratory tract.

Historical.—No definite description of the disease is to be found in the works of ancient writers. The disease was apparently separated as a clinical entity and described as such first by de Baillou. In 1578 he described an epidemic under the name of Tussis quinta. Despite the clarity of his picture, the disease continued to be confused with influenza till 1682 when Thomas Willis insisted on the epidemicity of tussis puerorum convulsiva seu suffocativa. Sydenham in 1679 also gave a clear picture of the disease. From this time on, and continuing up to the present time, whooping-cough has been the subject of much careful study and more controversy in medical literature. The specific exciting cause was not discovered till 1906.

Distribution.—"Whooping-cough is world wide in its geographical distribution. No climate, country or race seems to be immune to this disease although its extent and fatality vary greatly in different countries."* Combining the statistics of 24 countries for a recent five year period, Crum found that 1 per cent. of the grand total of deaths from all causes was due to whooping-cough. The disease is epidemic in all large centers of population, but epidemics are of frequent occurrence. In view of the fact that the greatest morbidity and mortality occur before the fifth year of life, epidemics in any given locality recur at frequent intervals. No race appears to enjoy an immunity to the disease, but it is noteworthy that the negro has a much higher mortality than the white. Thus, according to Crum,† at ages under one year the average negro death rate was nearly three times as high as the white death rate, while at ages one to four years the average negro death rate was nearly five times as high as the white. It is recognized today that whooping-cough is a widespread and very serious disease and much careful study has been given to its statistics. While the insertion of many detailed tables would be out of place in such an article as this, certain important facts stand out prominently. Most writers are in agreement concerning the figures. The summaries here presented are in the main taken from Crum's studies.*

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* Crum, Statistical study of whooping-cough, American Journal Public Health, v (1914), p. 994.

† *Ibid.*

The mortality from whooping-cough is decidedly higher among female than among male children. Thus in the Registration Area of the U. S. for the years 1900–1911 (inclusive), the death rate in female children from pertussis averaged 12.5 per 100,000 per year, as against 10.5 for males. The same excess is noted in the British and Bavarian Tables. It is interesting to note that Creighton explains this difference on the basis of anatomical and physiological difference: The less perfect development of the posterior space of the glottis in the female. The greatest mortality and the greatest incidence occur before the fifth year of life. Thus the death rate in Massachusetts in the first year of life was more than 2½ times the death rate in the second year of life.

Boudreau† points out that in Ohio, and in the Registration Area 50 per cent. of all deaths occur in children under one year of age, 95 per cent. of all deaths occur in children under five. Writing in 1916, he shows that the latest available mortality statistics (deaths per year) were as follows:

Ohio	500
Registration Area	6,145
United States (over)	10,000

Unlike measles, whooping-cough at present, appears to have a higher death rate in rural than in the urban area (Registration States).

The accompanying charts tabulated by the Prudential Life Insurance Co. of America (to whom acknowledgment is gratefully made) show:

1. Mortality from whooping-cough, U. S. Registration Area.
2. Mortality from whooping-cough, 15 representative American cities.
3. Mortality (for 100 years) from whooping-cough, all ages.
4. Average weekly case rates from whooping-cough, New York and Philadelphia.

Seasonal Influences.—In the Registration Area March, April, May, June, July and August are months of greatest incidence and highest mortality.

Summary of the Age Incidence.—The greatest susceptibility is from six months to five years of age. During the first months of life the disease is not common, but even the newly born are not immune.

The disease may occur at all ages however, and adults may contract the disease. It even occurs in old age. The immunity acquired by an attack is lasting. While the general incidence of the disease is great, natural immunity does exist, for the disease is not as common as measles. Van Sholly, Blum and Smith* studying the case records from a New York Clinic found that partial immunity to pertussis was exhibited by 31.6 per cent. of families. Fifty-eight per cent. of children in partially immune families escaped the disease after exposure. While these authors admit that their series was not large enough to warrant the drawing of sweeping conclusions, their findings are in accord with the generally accepted view that some degree of material immunity to pertussis does exist.

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* *Loc. cit.*

† Boudreau, Whooping-cough in Ohio, Ohio State Medical Journal, xii (1916), p. 557.

Specific Etiologic Factor.—All sorts of theories have been advanced as to the cause of the disease, and in recent years various organisms have been discovered and described as being the specific agents. It is now generally accepted that the specific organism is the one first discovered by Bordet and Gengou in 1900 and cultivated and intensively studied in 1906. The work of these investigators had been confirmed by Mallory and others.

The organism is present in great numbers between the cilia of the epithelium lining the trachea and bronchi. It is most abundant in the catarrhal stage and has rarely been found later than the first week of the paroxysmal stage.

The Bordet and Gengou bacillus is a short, oval non motile rod. It varies in size: From 0.2 to 0.3 μ in diameter, and from 0.5 to 2.0 μ in length. It occurs singly or in twos, exceptionally in short chains. It is aërobic, facultative anaërobic.

It grows best on the Bordet and Gengou medium: Glycerin, potato, blood agar, but transplants will grow on other media.

It resembles the influenza bacillus, though it is more regularly ovoid and somewhat larger than the Pfeiffer bacillus, and shows less tendency than the latter to pleomorphism and involution. It is Gram-negative and with appropriate stains shows bi-polar staining.

The organism shows similar cultural reactions to B. Bronchosepticus (bacillus of dog distemper).

Ferry and Noble† comment on this fact. They also showed close agglutination reactions between the two organisms.

Symptomatology.—The usual division of the symptoms into three stages: (1) Catarrhal, or stage of invasion, (2) paroxysmal or spasmodic and (3) stage of decline, or defervescence, is justified in the majority of cases. It should be noted, however, that the several stagse are not always sharply delimited, and that in atypical cases (formes frustes) they do not all occur.

The catarrhal stage sets in with the usual symptoms of acute respiratory catarrh. Malaise, dry cough, conjunctival irritation and sneezing are generally present. In the very early stage there may be subfebrile temperature (100°F.) but this usually disappears before the paroxysmal stage sets in. One point of importance, diagnostically, at this time, is that in the presence of a distinctly irritative cough, physical signs of bronchitis are apt to be missing. Despite the negative physical find the cough tends to increase in frequency and severity. The cough is usually much worse in the night than in daytime. This stage ordinarily lasts from one to two weeks. In the later period of the catarrhal stage, children tend to become physically quieter because they learn that activity produces more frequent and more severe coughing spells.*

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* Van Sholly, Blum and Smith, Journal A. M. A., lxviii (1917), p. 1451.

† Ferry and Noble, Journal of Bacteriology, iii (1918), p. 193.

Paroxysmal Stage.—The catarrhal symptoms disappear, the cough becomes more and more paroxysmal, until finally, the distinctive whoop appears. A single definite paroxysm with whoop is enough to make the diagnosis absolute, for the picture of the paroxysm is pathognomonic. After a short pause in breathing, a deep inspiration is taken. Then comes, without inspiration, a series of short, sharp rapidly repeated barks. These loud expiratory efforts convulse the entire body. The face becomes livid, the eye balls protrude, the veins of the head and neck stand out prominently. The tongue, swelled and deeply cyanotic, is protruded from the mouth during the paroxysm. Finally after a succession of such noisy explosive coughs, there follows a long crowing inspiration with the characteristic "whoop." Immediately thereafter there is a repetition of the expiratory coughing phase, to be ended again with the whoop. A single paroxysm may thus include five or even ten cycles. At the close of the attack, with choking and very often vomiting, a small globule of mucus is expelled, glairy and very tenacious. Children old enough to describe their sensations often speak of prodromes preceding the paroxysms, either choking or sneezing, or of a sense of weight or constriction about the chest. Such children will run to an elder for support or will grasp some firm object, or, failing these, will brace hands on knees. The terror of the children just before and during the attacks, often most distressing to witness, is in striking contrast to the calmness with which they resume their speech or play when the attack is over. While after very severe or very frequently repeated attacks the children may show marked lassitude and depression, this is certainly not the rule. As a matter of fact robust children appear to be subjectively better during the paroxysmal than during the catarrhal stage. Between paroxysms they appear normal and in good health.

Owing to the force with which the abdominal press is set during the paroxysm, involuntary evacuation of urine and feces often occurs, while, as has been said vomiting frequently ends the attack.

The duration of the attacks varies from a few seconds to 10 or even 15 minutes. The number of paroxysms varies from 15 to 20 to over 150 in the 24 hours.

The attack may occur spontaneously or may be induced by an irritation of the naso-pharynx. The imitative factor in childhood is often well illustrated in whooping-cough wards, where an attack in one child may be followed at once by paroxysms in all of the patients. Indeed this imitative feature is so marked that at one time whooping-cough was classed as a definite "neurosis." Paroxysms are apt to vary in intensity: As a rule a mild attack is followed by a severe one.

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* Abt, Archives of Pediatrics, xxxiii (1916), p. 881.

At times the whoop disappears as a result of intercurrent infections such as pneumonia, meningitis, vaccinia and diphtheria.

The spasmodic stage itself is marked by distinct periods, increase, fastigium and decline of the number of paroxysms. A simple chart kept by mother or nurse is thus often of value in determining the stage of the disease.

Physical examination after a prolonged paroxysm shows signs of temporary emphysema. The right heart is often dilated and there is evidence of congestion in the pulmonary circulation. This congestion gives rise to marked venous engorgment of the whole respiratory tract and explains the small hemorrhages that sometimes occur. Subconjunctival hemorrhages are particular common. Most authors consider this to be a purely mechanical effect of the coughing, but Luttinger believes that it is a specific reaction to the toxins liberated by the Bordet and Gengou bacillus. The paroxysmal stage lasts from four to eight or even twelve weeks.

The stage of decline is marked by gradual diminution in the number and severity of the attacks. The cough tends to return to the type of the catarrhal stage, though emotional excitement or indigestion may bring on a severe paroxysm. This stage ordinarily lasts from one to three weeks. But for some weeks thereafter, paroxysmal cough without whoop may persist, especially at night. This cough, to which the name "pertussoid" has been given is due to the enlargement of the tracheobronchial lymph-nodes, present in nearly all severe cases of pertussis (see below).

Gastro-intestinal System.—The sublingual ulcer or the ulcer of the frenum, formerly considered as diagnostic of whooping-cough, is found in other convulsive coughs of children. It is frequently missing in pertussis and is certainly not pathognomonic of the disease.

Catarrhal conditions of stomach and bowel are frequently found, usually a simple gastro-enteritis. Vomiting occurs very frequently at the end of the paroxysms, purely reflexly. As paroxysms occur very often after meals, the child often loses a great part of the food just taken. This vomiting is usually not accompanied by nausea, indeed just after a paroxysm with profuse vomiting the child may take a good deal of food at once, with evident relish and without discomfort. Prolapse of the rectum frequently occurs during the paroxysms.

Respiratory System.—Respiratory affections will be considered in detail under complications.

The Blood.—There is constant leukocytosis, occurring early and continuing through the paroxysmal stage, the degree of the leukocytosis bearing definite relation to the severity of the infection. As a rule this leukocytosis is of the lymphocytic variety. The percentage of lymphocytes may be high, up to 60 to 70 per cent. of the total number of whites. Meuniere, who first called attention to this, considered it as a definite diagnostic sign. Aside from the fact that young children normally show a much higher lymphocytic figure than do adults, it is to be remembered that enlargement of the tracheobronchial lymph-nodes is present in all severe cases of pertussis. And the very high lymphocytosis is to be explained on the basis of this lymph-node irritability.

The Urine.—Transient albuminuria is common in the catarrhal (febrile) stage. Sugar is found in about 10 per cent. of all cases, the glycosuria being transient. No explanation of this phenomenon has been offered, save that Burdetti claims that the glyogenic function is lowered in pertussis.

The Skin.—Various purpuric rashes are found and eczema is rather common.

Atypical Forms.—In institutions where epidemics of pertussis occur, it is not uncommon to find children showing paroxysmal cough without whoop. Such cases cause much difficulty in diagnosis, for they may be foci for the further spread of the infection. Until the advent of the complement fixation test (*q.v.*) the definite diagnosis in such cases was often a matter of impossibility. In very young infants the catarrhal stage is frequently greatly shortened, and the paroxysmal stage is characterized by the lack of a very definite whoop. Adults who have been exposed may show such mild paroxysms, without definite whoop, that the diagnosis is difficult. Here too the comple ment fixation test is of distinct value.

Duration.—Average cases run their course in from 6 to 10 weeks without treatment. The persistent cough that lasts for many weeks after the subsidence of all paroxysms is often due to persistence of enlarged tracheobronchial glands. The constitution of the child, the season of the year, the genius of the particular epidemic are all factors of importance in determining the length of the attack. Marked variations in severity, course and duration of the disease are often encountered in children of the same family. And finally, it is to be remembered that affections of the respiratory tract are peculiarly liable to follow pertussis and are responsible for the continuance of the cough in many instances.

Complications.—Certain of these come under the category of mechanical insults to the organism occurring as the direct results of the physical violence of the paroxysms. In this class come the subconjunctival hemorrhages, epistaxis, hemorrhage into the thyroid, etc. The marked degree of pulmonary emphysema sometimes found can also be mechanically explained. Umbilical or inguinal hernia may be due to the greatly increased abdominal pressure.

The complications of greatest importance, on account of their frequency and severity, are those of the respiratory system.

Bronchopneumonia is of frequent occurrence in the paroxysmal stage. It is the great factor in the high mortality of pertussis in infancy and earliest childhood. It begins most often as a bronchitis, the process extending rapidly through the bronchial tree, until a capillary bronchitis with patches of consolidation has resulted. Weak children of any age, children whose resistance has been lowered by some antecedent infection, are apt to have their whooping-cough complicated by bronchopneumonia. Its onset is often insidious and the physical signs not well marked in the earlier stages. But a rise in temperature during the paroxysmal stage, unless it can be definitely explained otherwise, should always excite the suspicion of beginning bronchopneumonia. There appears to be, also, a tendency to relapse in the bronchopneumonia of pertussis.

Reference has already been made to the fact that enlargement of the tracheobronchial lymph-nodes is found in nearly all severe cases of pertussis. In many cases this is a simple adenitis, *not* tuberculous. The physical signs of interscapular dullness, signs of pulmonary compression, are usually distinct. The *x*-ray shows the enlarged glands in young children, even where there is no caseation or fibrosis. And the marked lymphocytosis affords confirmatory evidence. It is this tracheobronchial adenitis which causes the prolongation of the cough for weeks and weeks after the paroxysms have subsided. But, in addition, these inflamed bronchial glands frequently become the seat of tuberculous infiltration, from which pulmonary tuberculosis frequently arises. Or an existing, but latent, tuberculosis of glands or lungs may be lit up by an attack of whooping-cough. The mortality from whooping-cough directly is very great; its indirect mortality resulting from the predisposition to tuberculosis that it induces is also very high. Among rarer respiratory complications should be mentioned bronchiectasis, mediastinal, subpleural (and secondarily) cutaneous emphysema. Edema of the glottis occurs at times.

Circulatory System.—Acute dilation of the right heart is not at all uncommon and a mild degree of myocarditic degeneration not infrequently follows the disease, especially in its severe forms.

Nervous System.—The most frequent complications of the central nervous system are convulsions. They occur more commonly in infancy and early childhood. The clonic-tonic spasms may involve either limited muscular areas or all of the voluntary muscles. They are attended by loss of consciousness and are sometimes fatal.

Hemiplegias and monoplegias from cerebral hemorrhage, due to extreme engorgment of the cerebral vessels during paroxysms have also been reported. Encephalitis, optic neuritis (Strümpell) and hemorrhage into the internal ear causing permanent deafness are among the rarer complications. French writers also describe a series of psychoses as occurring at times, though rarely.

Association with Other Diseases.—Pertussis lowers the resistance of children to such a degree that they often fall prey to other infections during an attack. The diseases most commonly associated with whooping-cough are measles, diphtheria and scarlet fever.

Diagnosis.—The diagnosis of whooping-cough in typical cases during the paroxysmal stage is exceedingly simple. The spasmodic staccato cough with the characteristic whoop, form a diagnostic symptom group, which is pathognomonic. Also it should be remembered that typical attacks can at times be induced early in the paroxysmal stage by gently irritating the posterior wall of the pharynx with a spoon or tongue depressor and this device may succeed in clearing up a diagnosis at once.

The difficulty lies in making a diagnosis in the catarrhal stage, especially in institutions where children are segregated. The importance of preventing epidemics of pertussis in foundling asylums, childrens' homes and childrens' hospitals, in schools, is manifest.

Certain findings have diagnostic value in the catarrhal stage.

(*a*) Cough, increasing in severity, with absence of the ordinary signs of bronchitis on physical examination.

(*b*) The presence of a lymphocytic leukocytosis.

(*c*) The history of exposure, or the presence of an epidemic without definite history of exposure.

(*d*) The tendency of the cough to be worse at night.

But as will readily be seen, these findings singly or together cannot do more than offer presumptive evidence of the nature of the cough. In recent years therefore, much attention has been paid to the diagnosis of whooping-cough, in the catarrhal stage, by means of modern laboratory methods. Of these, three are of particular importance, and demand special consideration, *viz.:*

1. Identification of the causal organism from the sputum, by morphological and cultural characteristics.
2. Complement fixation test.
3. Agglutination test.

1. Identification of the Specific Organism from the Sputum.—It is now generally admitted that the Bordet and Gengou bacillus is found in the trachea and bronchi of affected children in largest numbers in the catarrhal stage. Chievitz and Meyer* point out that after a patient has whooped for a month the bacillus disappears from the sputum. In a series of cases examined, these authors found the bacillus in every case after two weeks of paroxysms.

It was present in 24 of 33 cases which had been whooping 2 to 3 weeks
9 of 27 cases which had been whooping 3 to 4 weeks
3 of 27 cases which had been whooping 4 to 5 weeks
1 of 42 cases which had been whooping over 5 weeks.

The French authorities are so thoroughly convinced of the fact that the bacillus disappears from the sputum after the paroxysmal stage has lasted a month, that in March, 1916, the French Ministry of Public Instruction issued an order permitting children with whooping-cough to return to school after they had whooped a month.

The isolation of the organism from the sputum is not easy. Young children do not expectorate, but swallow their sputum. Chievitz and Meyer have described an original method of obtaining the bacillus in pure culture. Petri dishes, loaded with appropriate culture medium are held, open, 4 in. from the mouth of the patient during cough.

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* Chievitz and Meyer, Bacteriol. of whooping-cough, Annales de l'Inst. Past, xxx (1916) p. 503.

The Petri dish is thus inoculated by droplet. Collected and inoculated in this way, B. Pertussis is said to grow with unusual strength and readiness.

It would seem that by this method, early detection of B. Pertussis in the sputum of suspected cases would be greatly facilitated and the chance of a definite diagnosis in the catarrhal stage greatly enhanced.

2. Complement Fixation.—When Bordet and Gengou described the bacillus of pertussis in 1907 they used the complement fixation test to control their bacteriologic findings. They found that the serum of patients convalescent from pertussis, and for some time thereafter, would show definite fixation of complement with an antigen of pure culture of B. Pertussis. From this time on much work has been done by various observers with the complement fixation test. The difficulty has been that fixation of the complement apparently did not occur early. In 1911 Bordet and Gengou reported that fixation was not seen early, that in general "it did not show itself markedly till toward the period of convalescence or cure."

Later work however, has shown that complement fixation does occur early. In 1914 Wagner and I* published two papers reporting the results of our studies. We used *active* serum, with Noguchi hemolytic system. Our antigen was a saline emulsion of a 72 hour growth of the Bordet and Gengou bacillus on ascitic fluid agar. We obtained a positive complement fixation test in all 18 cases tested in the paroxysmal stage; of 12 cases in the catarrhal stage, from one to five weeks before the whoop, 11 gave positive reactions. Sixteen normal individuals were negative. Other observers had different results. Commenting on the variations found with reference to the reliability of the test Olmstead and Luttinger† remark that "the variation in the results of different workers may be explained partly by difference in technique such as, method of preparing antigen, amount of antigen used in test, amount of serum used in test, use of active or inactive serum, time and temperature allowed for fixation, etc." These authors report an extensive series of cases studied and their summary and conclusions are here given in full.

1. The most reliable antigen for complement fixation tests in whooping-cough is obtained by autolyzing an aqueous emulsion of 24 to 48 hour growth of the Bordet and Gengou bacillus for 18 to 24 hours at 56°C. and shaking for several hours. The closeness of the Bordet and Gengou strains is still under investigation. To obtain the maximum number of positive reactions it may be necessary to use a polyvalent serum.

2. An active serum may give non-specific positive reactions. A negative reaction given by active serum is stronger evidence of the lack of an infection than is a negative reaction by an inactive serum.

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* Friedlander and Wagner, Diagnosis of whooping-cough by the complement deviation test. Journal of American Medical Ass'n, lxxii (1914), p. 1008; American Journal of Diseases of Children, viii (1914), p. 134.

† Olmstead and Luttinger, Complement fixation in pertussis, Archives of Internal Medicine, xvi (1915), p. 67.

3. For fixation one-half hour in the water-bath or one hour in the incubator is absolutely reliable. Ice-box fixation probably gives reliable results: The optimum period is still to be determined. Fixation at room temperature for four hours is unsatisfactory, at least in rooms with variable temperature.

4. About 40 per cent. of whooping-cough cases have given a positive reaction with antigens of the Bordet and Gengou bacillus when inactive serum was used. The highest percentage of positives is given by convalescent vaccinated cases. Ten per cent. of whooping-cough cases have given positive reaction with antigens of hemoglobinophilic strains.

5. A ++, +++, or ++++ reaction by inactive serum with an antigen of Bordet and Gengou bacillus is diagnostic of whooping-cough, A+ or ± reaction is suspicious, a negative reaction has little significance.

Conclusions.—Complement fixation tests in serum from 111 cases of pertussis or suspected pertussis support the theory that the Bordet and Gengou bacillus is the etiological factor of the disease. The complement fixation test may be of value in the diagnosis of doubtful cases of pertussis.

3. Agglutination Test.—Studies in agglutination tests have hardly gone far enough as yet, to afford much diagnostic data. In a review of work done, and as a result of their original studies, Povitsky and Worth* conclude that "agglutination test in clinical diagnosis of pertussis compares favorably with complement fixation only in the first week of the whoop." In the later stages of the disease complement fixation antibodies appear more frequently than agglutinins.

Thirty-three per cent. of adult non-pertussis sera show agglutination up to 1:40: 17 per cent. in up to 100: 40 per cent. of children's non-pertussis sera (scarlet fever cases) showed a reaction in up to 1:40. A dilution of not less than 1:200 is necessary for a practically positive diagnosis of pertussis by agglutination test.

Summarizing laboratory methods of diagnosis, it may be said that the difficulty of obtaining the specific organism early from the child's secretion, can be greatly reduced by the use of the Petri dish method of Chievitz and Meyer. Their procedure is simple and if their results can be confirmed by further study and more wide spread use, early diagnosis can be helped.

The complement fixation test is of real worth, and as its technique is codified it will doubtless come into more extensive use. If, as seems likely, it can be worked out to the degree that it gives positive results in the catarrhal stage, results that may be depended upon diagnostically, a big step forward will have been taken.

The agglutination test has, as yet, not yielded results of great promise in early diagnosis.

Prognosis.—A disease which kills 10,000 children a year in the United States alone must be regarded as a serious scourge. The

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* Povitsky and Worth, Agglutination in pertussis, Archives of Internal Medicine, xvii (1916), p. 279.

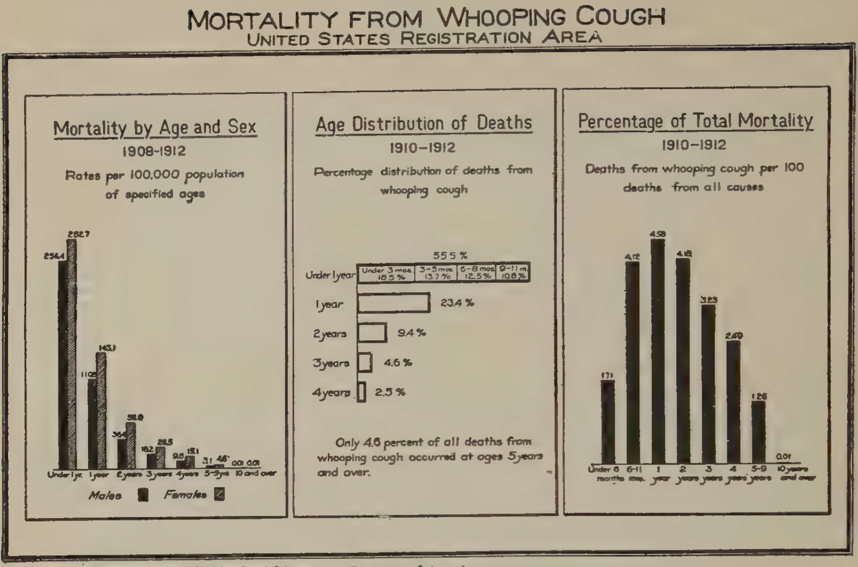

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FIG. 9.

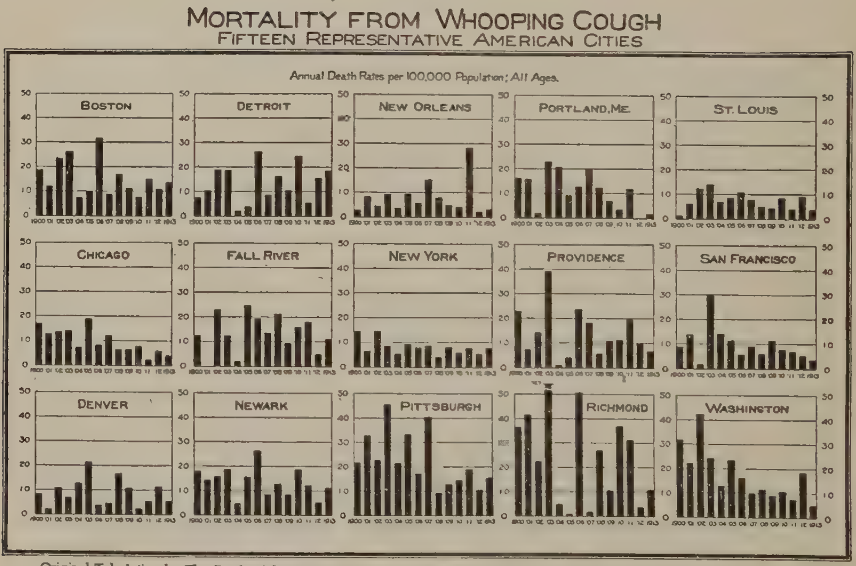

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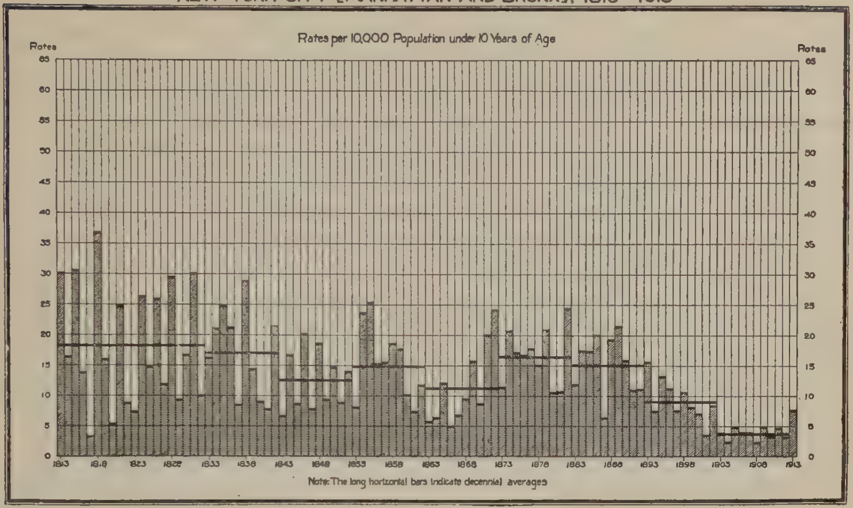
FIG. 10.

MORTALITY FROM WHOOPING COUGH, ALL AGES
NEW YORK CITY [MANHATTAN AND BRONX], 1813–1913



Note: The long horizontal bars indicate decennial averages

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FIG. 11.

AVERAGE WEEKLY CASE RATES FROM WHOOPING COUGH
NEW YORK CITY AND PHILADELPHIA. 1906–1912

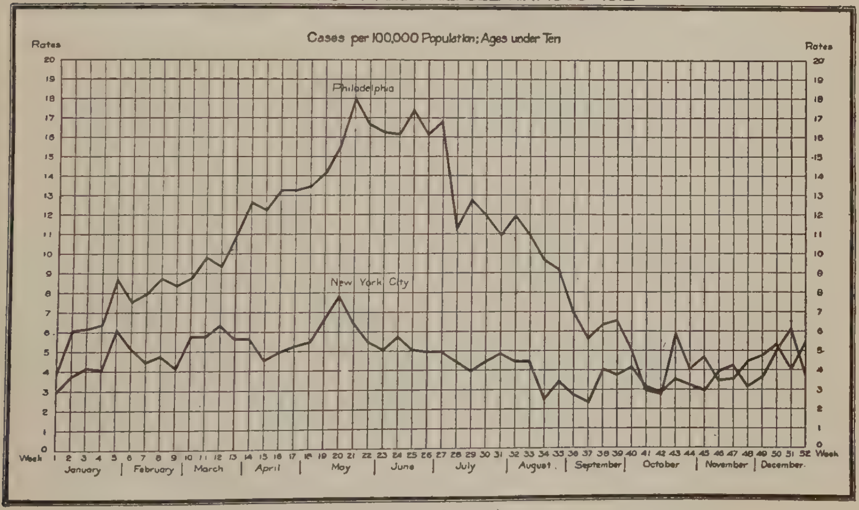

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FIG. 12.

seriousness of this disease is fully appreciated by hygienists and sanitarians. The mass of the profession and the laity even now do not seem alive to its real dangers. As Rucker has pointed out "If bubonic plague were to kill that many children (10,000) in the United States in one year the whole world would quarantine against our country. A child dead of a whooping-cough is just as dead as a child dead of plague."

The great mortality from whooping-cough, of course, comes in children under five years of age. As had been stated 95 per cent. of all deaths from pertussis comes in the first hemi-decade of life. Indeed, 50 per cent. of the deaths come in children under one year of age. Therefore in institutions where infants and young children are segregated, epidemics of whooping-cough are particularly to be dreaded.

In older children the outlook is of course, very much more favorable, but it must not be forgotten, that even in older children, pertussis frequently lights up latent tuberculosis.

The disease is very rarely fatal in adults.

Mortality tables, compiled by the Prudential Life Insurance Co. are herewith appended. They require no special discussion, but point their moral very distinctly.

(*a*) Comparative mortality from whooping cough in 17 countries.

(*b*) Proportionate mortality from whooping-cough Registration Area, United States, 1910–1912.

(*c*) One thousand fatal cases of whooping-cough showing primary complications.

(*d*) Deaths complicated with respiratory and digestive diseases, 1000 deaths from whooping-cough.

Comparative Mortality from Whooping-cough in 17 Countries

Country	1883–1887			1908–1912			Increase or decrease in rate
	Population	Deaths	Rate	Population	Deaths	Rate	
Australia	13,327,248	2,351	17.6	21,974,430	1,574	7.2	−10.4
Austria	114,323,956	119,206	104.3	142,091,028	47,036	33.1	−71.2
Belgium	29,243,761	19,056	65.2	37,070,103	11,650	31.4	−33.8
Ceylon	14,076,141	391	2.8	20,200,235	382	1.9	− 0.9
Denmark	10,382,000	1,351	13.0	13,678,000	1,336	9.8	− 3.2
England and Wales	136,120,085	59,240	43.5	178,978,660	42,081	23.5	−20.0
Ireland	24,699,974	7,916	32.0	21,925,004	5,277	24.1	− 7.9
Jamaica	2,989,079	3	0.1	4,220,187	1,505	35.7	+35.6
Massachusetts	9,793,350	1,234	12.6	16,832,078	1,941	11.5	− 1.1
Netherlands	21,542,127	6,444	29.9	29,602,284	5,663	19.1	−10.8
New Zealand	2,833,735	774	27.3	4,963,561	258	5.2	−22.1
Norway	9,694,600	1,324	13.7	11,683,500	1,680	14.4	+ 0.7
Ontario	9,000,000	798	8.9	11,805,519	1,282	10.9	+ 2.0
Prussia	141,183,802	72,663	51.4	199,629,445	47,584	23.8	−27.6
Scotland	19,282,219	12,730	66.0	23,528,940	10,190	43.3	−22.7
Sweden	23,305,010	4,159	17.8	27,029,454	3,940	14.6	− 3.2
Switzerland	14,480,395	2,944	20.3	18,458,916	2,903	15.7	− 4.6
Total	596,277,482	312,584	52.4	783,671,344	186,282	23.8	−28.6

PROPORTIONATE MORTALITY FROM WHOOPING-COUGH, REGISTRATION AREA, UNITED STATES, 1910–1912

Age	Deaths from		Percentage of the total mortality due to whooping-cough
	All causes	Whooping-cough	
Under 6 months	346,671	5,931	1.71
6 to 11 months	104,479	4,302	4.12
Under 1 year	451,150	10,233	2.27
1 year	94,155	4,313	4.58
2 years	41,496	1,736	4.18
3 years	25,976	840	3.23
4 years	18,663	465	2.49
Under 5 years	631,440	17,587	2.79
5 to 9 years	53,329	673	1.26
10 years and over	1,794,971	178	0.01
Ages unknown	3,207	9	
All ages	2,4829,47	18,447	0.74

ONE THOUSAND FATAL CASES OF WHOOPING-COUGH, SHOWING PRIMARY COMPLICATIONS

(Prudential Industrial Mortality Experience, 1911–1913)

Complications	Males		Females		Both sexes	
	Number of deaths	Per cent. distribution	Number of deaths	Per cent. distribution	Number of deaths	Per cent. distribution
Bronchopneumonia	140	28.3	146	28.8	286	28.6
Pneumonia	125	25.3	145	28.6	270	27.0
Bronchitis	28	5.7	28	5.5	56	5.6
Other respiratory diseases	10	2.0	5	1.0	15	1.5
Meningitis	27	5.5	17	3.4	44	4.4
Cerebral congestion	3	0.6	6	1.2	9	0.9
Heart complications	10	2.0	15	3.0	25	2.5
Digestive complications	43	8.7	36	7.1	79	7.9
Nephritis	2	0.4	6	1.2	8	0.8
Dysentery			6	1.2	6	0.6
Tuberculosis of lungs	4	0.8	5	1.0	9	0.9
Other miscellaneous	22	4.5	23	4.6	45	4.5
No complications	80	16.2	68	13.4	148	14.8
Total	494	100.0	506	100.0	1000	100.0

DEATHS COMPLICATED WITH RESPIRATORY AND DIGESTIVE DISEASES—ONE THOUSAND DEATHS FROM WHOOPING-COUGH
(Prudential Industrial Mortality Experience, 1911–1913)

Age	Total of whooping cough deaths	With respiratory complications		With digestive complications	
		Number of deaths	Per cent. of total	Number of deaths	Per cent. of total
1 year	543	318	58.5	66	12.2
2 years	184	120	65.2	6	3.3
3 years	126	83	65.9	5	4.0
4 years	56	45	80.3	—	—
5 to 9 years	81	56	69.2	1	1.2
10 to 19 years	9	5	55.6	1	11.1
20 years and over	1				
Total	1000	627	62.7	79	7.9

Prophylaxis.—Until very recently it has been universally held that no prophylactic measures other than isolation of suspected cases could be of avail. Today such a view is not tenable. The modern treatment of whooping-cough with vaccin, has proved itself of great value in preventing the spread of the disease in institutions, and among those exposed to the disease. There is reason to believe now that in vaccin therapy we possess an agent of great prophylactic and curative value. The subject will be more fully discussed under the head of specific therapy.

Treatment.—No disease has had a larger list of remedies proposed and enthusiastically lauded as "specifics" than pertussis. As one of the curiosities of medical literature may be noted the fact that a recent writer on the subject actually collected and listed 400 drugs and therapeutic measures supposed to be beneficial.

Certain general hygienic measures are of real importance. The child should lead as quiet a life as possible, free from excitement. Weather permitting, it should be out of doors a great part of each day and the sleeping room should be especially well ventilated. Particular care should be taken to protect the child from dust clouds, strong winds and irritating vapors. The clothing should be warm. Care should be taken to have the bed warmed at night. Cold sheets are particularly apt to bring on paroxysms when the child comes in contact with them.

The diet should be light but nutritious. Where vomiting is severe, milk diet is often very well borne. When a meal is lost by vomiting, another should usually be given at once. Small quantities of food, rather frequently given, are ordinarily better borne than three large meals a day. Excessive vomiting is often controlled by a rather tight abdominal binder. Kilmer has perfected a stockinette band, which answers very well. Various sprays and inhalations have been strongly recommended. It is doubtful whether any of these are of real value. Where there is excessive irritability of the nose and throat inhalations of compound benzoin or of creosote or oil of eucalyptus vapor may give relief.

Internally all sorts of antispasmodics have been recommended. Certain it is that opiates in appropriately small doses, give much relief. Heroin, papaverine, the old English preparation of the bimeconate of morphine all have their uses in extreme cases. They should not be used too frequently and should not be incorporated with antispasmodic mixtures to be used routinely.

Quinin, first recommended in pertussis by Binz has enjoyed great favor. His formula of 1 cg. (1/6 gr.) for each month of the child's age, 1 dg. (1½ gr.) for each year, has been rather generally adopted. Such doses are given three or four times daily.

The safest antispasmodics are the bromids and belladonna. The belladonna given as the tincture is ordinarily well borne and in rather large doses proportional to the age.

Bromid of soda deservedly enjoys a reputation as an antispasmodic. A combination of bromid of soda with antipyrin makes an excellent mixture, which can be given once, twice, or even three times during the night to secure rest. Care should be taken to see that the dose of antypyrin is not too large and it should not be used at all when the child's heart is weak.

Treatment of Complications.—No special discussion of the treatment of complications is needed. Bronchopneumonia is to be treated according to approved modern methods, remembering that tincture of strophanthus (½ to 1 drop doses) is a better cardiac stimulant for infants and very young children than is digitalis.

Specific Therapy.—The one great advance in the treatment of pertussis in the last few years has been the introduction of vaccin therapy. Sufficient evidence has now been accumulated and reported to prove that this is a real advance. It is not to be understood that vaccin therapy cures all cases at once, but properly used it certainly shortens the paroxysmal stage, diminishes the severity and frequency of the paroxysms and wards off complications.

Vaccin is of definite prophylactic as well as therapeutic value. There has naturally been diversity of opinion as to type of vaccin to be used, as well as to amount and time of its administration.

The attempt is therefore made here to give a resumé of recent contributions to these various phases of the subject.

It has been shown that pertussis vaccin is of value both in prophylaxis and treatment.

Prophylaxis.—Shaw* reports that at St. Margaret's House for infants in Albany, 164 children were exposed to pertussis in four epidemics. Only 7 per cent. of these children contracted the disease. Vaccin was administered from pure cultures of the Bordet and Gengou bacillus, prepared by the State Laboratory. Allowing for natural immunity, Shaw remarks that, from previous experience, at least 50 per cent. of these children would have succumbed to the disease without vaccin.

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* Shaw, New York State Medical Society Meeting, Utica (April, 1917).

Hoag* states that vaccin is effective at any stage of the disease, but that as a prophylactic it is absolute. He insists that every effort should be made to give it to children who have been exposed. He reported 17 children definitely exposed to the disease. All of them received vaccin and not one of them contracted pertussis.

In his most recent article on vaccin therapy Paul Luttinger† refers to this record of Hoag's which has heretofore not been equalled. He reports 51 cases (private practice) where vaccin was used prophylactically. Fourty-two of these (82 per cent.) developed no symptoms. Seven (14 per cent.) had a non-paroxysmal cough for two weeks and two (3.7 per cent.) went through a moderate attack of pertussis.

Even von Sholly, Blum and Smith‡ who are not overly enthusiastic as to the *curative* value of the vaccin believe that there is definite value in the prophylactic administration.

In his latest article C. J. Bloom§ states that as the result of his accumulated experience, the vaccin has definite value as a prophylactic. In general therefore it may be said that experience has shown that the vaccin is of real prophylactic value. It should be used in full doses, on children who have been exposed. And inasmuch as the diagnosis in early stages, is not easy, it should be used in suspicious cases. The earlier the vaccin can be given the more beneficial its results. If the complement fixation test can be so perfected as to be definitive in the catarrhal stage, a long step forward will be taken, because vaccin given at this time is undoubtedly more efficacious than in the paroxysmal stage. The work of the present author on this test, already referred to, is at least promising and further studies are now under way. Meantime it would appear to be the part of wisdom to use the vaccin in all exposed children and in suspicious cases without definite proof of exposure. All writers emphasize the fact that the danger of anaphylactic shock is minimal. Given as it should be, hypodermically and *not* intramuscularly, the vaccin causes very little local reaction and the pain of the injection is not great, certainly not of material moment.

It seems well within reasonable bounds to say that prophylactic vaccin therapy is an agent of very great value in checking the spread of this serious disease.

Therapeutic Injections.—In general it may be said that observers are now agreed that vaccin injection tend to shorten the duration of the paroxysmal stage and to diminish the number and severity of the paroxysms and to lessen the chances of complications. Luttinger* in his last report is most enthusiastic and emphatic in his stand in favor of vaccins. He reports 187 cases (private practice). Eleven of these were very severe cases, and in these 11 bromid of soda and antipyrin were given to allay the excessive irritability. No treatment other than vaccin (but including attention to general hygiene and feeding) was given. The average duration of the paroxysmal stage including the 11 very severe cases, was 16 days. The paroxysms were greatly shortened. *No* complications occurred, not even subconjunctival hemorrhage.

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* Hoag, American Medicine, xi (1916), p. 255.

† Luttinger, New York Medical Journal, cix (Feb. 22, 1919), p. 322.

‡ Von Sholly, Blum and Smith, Journal American Medical Association, lxviii (May 19, 1917), p. 1451.

§ Bloom, C. J., Archives of Pediatrics, xxxvi (January, 1919), p. 1.

Shaw† reports 112 cases treated with vaccin. Thirty-six per cent. were shortened, decidedly, in duration, 52 per cent. had fewer and less severe paroxysms and 12 per cent. were not affected.

Goler‡ reports 396 cases, Wolverton§ 36 cases and Loge|| 100 cases. The consensus of opinion of these authors is that the paroxysmal stage is shortened, the attacks less frequent and less severe.

Hoag¶ believes that vaccin seems effective at any stage of the disease and should be given though the patient is well along in the paroxysmal stage. The average duration of the paroxysmal stage treated with vaccin was 19½ days.

Bloom** emphasizes the fact that the use of vaccin minimizes the loss of weight, decreases the severity of the attack and prevents complications.

Type of Vaccin.—Most authors are agreed that vaccin prepared from pure culture of the Bordet and Gengou bacillus is preferable. Huenekens†† is of the opinion that vaccin freshly prepared, without preservative, is of greater value than stock preserved vaccin. He says that pertussis vaccin from two to three months old, even employed in maximum dosage immunizes in only 12.5 per cent. of cases. Vaccin two to four weeks old conferred immunity in 50 per cent. of cases, while freshly prepared vaccin showed evidence of antibody formation in 94 per cent. of all cases. He is therefore decidedly of the opinion that vaccin should be freshly prepared (less than one week old without preservative).

Aside from the difficulty of obtaining vaccin fresh at all times and at all places, it is to be noted that Huenekens' observations have not been fully confirmed.

There is abundant evidence to the effect that vaccin prepared from pure cultures of Bordet and Gengou bacillus (preferably polyvalent including different strains) are perfectly effective, even when preserved

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* Luttinger, New York Medical Journal, cix (Feb. 22, 1919), p. 322.

† Shaw, New York State Journal of Medicine (January, 1918).

‡ Goler, New York State Medical Journal (February, 1918).

§ Wolverton, American Journal of Clinical Medicine (January, 1917).

|| Loge, Therapeutic Gazette (Mar. 15, 1918).

¶ Hoag, *Loc. cit.*

** Bloom, *Loc. cit.*

†† Huenekens, E. J., Pertussis treated by vaccins American Journal, Diseases of Children, xvi (1918), p. 30.

in the usual way. Such vaccin is easily obtainable and may be used with full confidence.

There has been some discussion as to the relative value of pure culture and mixed culture vaccins. Of recent writers Bloom* is almost alone in his advocacy of mixed vaccin and even he now states that the only organism he advocates adding to the Bordet and Gengou bacillus is the influenza bacillus. As is well known there are morphologic and cultural similarities between the two organisms. And the work of von Sholly, Blum and Smith, already referred to, led them to believe that injections of influenza vaccin might have a beneficial effect on the course of a case of pertussis. Such a theory would be in harmony with the views of Vaughan.

The consensus of opinion however would seem to be that the reaction following the Bordet and Gengou vaccin is a specific one and summing up all the evidence, it would seem to the writer that this view is correct.

Dosage.—In the light of the recent work it seems fair to conclude that the early failures were largely due to insufficient dosage. The dosages as now universally used are very much larger than were formerly administered. Ordinarily now three doses are given, on alternate days, of one billion one and one-half billion and two billion respectively. These doses should be given as early as possible and irrespective of the age of the child. They should be given hypodermically (not intramuscularly) and under strict aseptic precautions. Luttinger notes that after the first injection the cough may be temporarily increased for one night, with marked subsidence in severity and number of attacks thereafter.

In very severe cases, Luttinger advocates the use of six injections instead of three. Dosage (for a child of one year) ½ billion, 1 billion, 2 billion, 4 billion, 8 billion and 16 billion. He allows an interval of five days between the third and fourth injections, otherwise the injections are given on alternate days.

For prophylactic use three injections will suffice.

X-ray Treatment.—Recently, the therapeutic value of *x*-ray treatment in the treatment of pertussis has been highly lauded.

The selective affinity of the *x*-ray for lymphatic tissues is well known. It has been a matter of common knowledge that tracheobronchial adenopathy can be successfully treated in many instances by the use of the roentgen ray. The irritative paroxysmal cough which is part of this affection—and to which the name "pertussoid" has been given—subsides very rapidly under *x*-ray treatment.

It is altogether probable that the good results which various observers have reported from the use of the *x*-ray in whooping cough is attributable to the shrinking of the enlarged tracheobronchial glands so frequently present in pertussis.

In substantiation of this view is the fact that under *x*-ray treatment the lymphocytosis disappears—the lymphocytosis is merely a manifestation of the adenopathy and not part and parcel of the pertussis.

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* Bloom, *Loc. cit.*

Insofar as the tracheobronchial gland irritation—with its resultant cough—can be allayed—the *x*-ray is of definite value in the treatment of pertussis. It is not to be regarded as specific treatment for the disease itself. It should not supplant the use of properly prepared vaccines but may—with great propriety be used in conjunction with them.

CHAPTER CXLIV

VARIOLA

By Heman Spalding, M.D.

Chicago, Ill.

Historical.—This aspect needs but slight notice, being practically identical with that of the disease in general. The principal dates of interest in connection with the subject are as follows: Variola has been recognized in China, India, and elsewhere in the Orient since long before the Christian era. An epidemic was described in France in the late 6th century, and in Ireland in A.D. 657. The first good description of the affection was furnished by Rhazes, the Arabian physician, early in the 10th century.

Variola was first used as a name for the disease by a French bishop (Marius of Avenche), in A.D. 570 (Auché). The term petite vérole (Smallpox) came into use in A.D. 1494, after the recrudescence of syphilis, the papular and pustular manifestations of which were termed grosses véroles (large pox). Not long after (1518) the term "smallpox," evidently translated from the French, came into use in England.

Shortly after the discovery of America (1507), variola was introduced into the West Indies, according to Hirsch. In 1649, an epidemic developed in Boston (Brown).

Inoculation was introduced into England by Lady Mary Wortley Montague in 1721. A few years before (1718) her three year old son had been inoculated in Turkey. Zabdial Boylston (of Boston) first performed inoculation in the U. S. in 1721, the same year it was brought to England.

The immortal Jenner, on May 14, 1796, performed the first vaccination on an eight year old boy—James Phipps; and in 1800 the procedure was introduced into the U. S. by Benjamin Waterhouse. In 1880, owing to the efforts of the late Ernest Hart, at that time editor of the *British Medical Journal*, the English government was induced to use calf-lymph, instead of arm-to-arm (human) vaccination, as was the custom hitherto.

Pathology.—The exhaustive account by Councilman, Magrath and Brinckerhoff of the pathologic anatomy and histology of variola is based on material derived from 54 necropsies, obtained during conditions which ensured prompt study and good preservation. As a rule, all organs of the body were inspected, regardless of the probable occurrence of lesions. The forms of variola met with are classified as follows: Variola vera, 47 cases; Variola pustulosa hemorrhagica, 2; Purpura variolosa, 4. The first of these is subdivided into—(*a*)

Uncomplicated, 37; (*b*) with hemorrhage, 2; (*c*) abortive, 2; (*d*) with complications, 6.

The findings are summarized as follows:

(*a*) Lesions in character and distribution fundamentally specific, and due to the presence of a parasite peculiar to the disease.

(*b*) Associated lesions, of indeterminate specificity, analogous in kind to those present in many infectious diseases, but in degree characteristic of variola.

(*c*) Lesions due to accessory etiologic factors, bacteria, the presence and activity of which are conditioned by the specific infection.

(a) **The Specific Lesion.**—(1) The specific lesion of variola is a focal degeneration of stratified epithelium, vacuolar, and accompanied by serous exudation and formation of a reticulum.

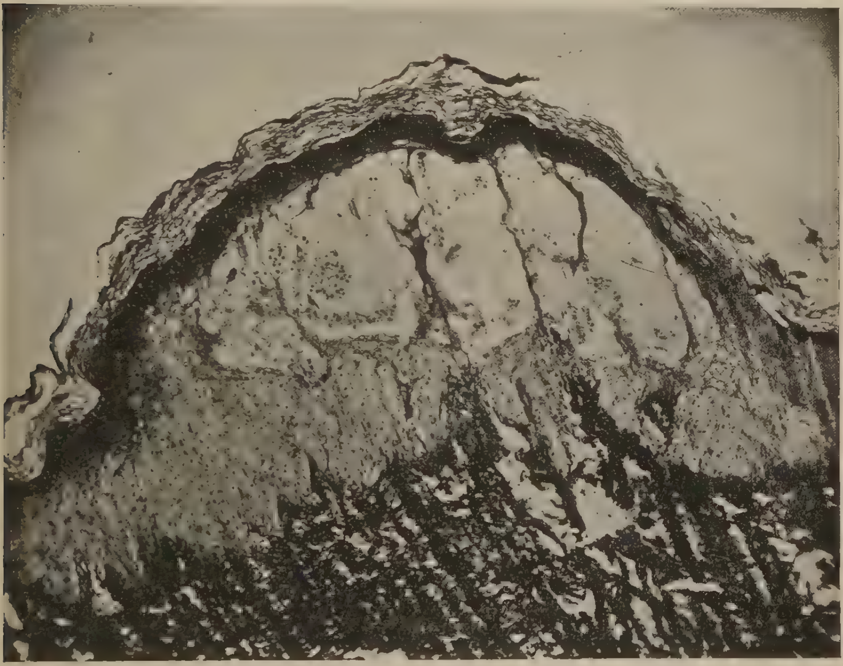

Fig. 13.—Small-pox pustule. The pustule is formed in the substance of the epidermis. Strands of persistent epithelial cells cross it. (Dr. James.)

2. The fully-developed product of these processes is a characteristic multilocular pock or pustule.

3. The occurrence of these lesions is sharply limited to the stratified epithelium of the skin, and of the mucosæ of soft palate, pharynx and esophagus.

4. In number the skin lesions may be very few, or so numerous as to overspread the entire body. In distribution they are fewest on the lower trunk and most numerous on face and hands. They bear no

fixed relation to any anatomic structure in the skin. In size, even when fully developed, they vary widely.

5. The lesions appear on about the fourth day, and passing through progressive stages reach a climax of development on the eighth or ninth day. Their appearance on all parts is not simultaneous, but beginning on face and hands, extends thence to the trunk and the extremities.

6. The typical lesion, best seen in the skin, begins with degeneration of the cells in the lower layers of the epidermis, accompanied by exudation at first serous, later more or less cellular, the products of which are contained within a reticulum formed by the degenerated cells. The exudate increases and the spaces of reticulum enlarge until its fibres finally rupture, and the lesion becomes a filled-out pustule. This development may take place within the epidermis, and the fluid contents of the pock be separated from the corium by relatively intact cells; or the corium may form the bottom of the pustule, when there is usually necrosis of the papillary border.

7. The subsidence and repair of the lesion are accomplished by removal of the fluid portion of the exudate by absorption and drying, and by regeneration of the epidermis. During this latter process, the residual mass of degenerated epithelial cells, leukocytes and débris, enclosed between two layers of horny epidermis, the old and the newly formed, is exfoliated. The complete evolution occupies about two weeks.

8. Edema, cellular infiltration and hemorrhage of the corium may be associated with the lesions of the epidermis.

9. The lesions of the mucosæ are in degree proportional to the extent and severity of those in the skin. At an early stage they resemble the latter, but owing to the structure, the resemblance is lost in their evolution. In the absence of the horny restraining layer, the degenerated epithelial cells are cast off, and the vesicle within the epidermis is rarely seen, the pustule never.

10. Contained within these lesions of skin and mucosæ, and determining their specificity and occurring chiefly within the cells of the rete mucosum is the parasite peculiar to variola. No parasites have been found in any lesions of the skin in which repair was well advanced.

11. Accompanying the specific lesions and simulating them in form are others—bleb-like—in which the entire epidermis is elevated by fluid exudate; in these the parasite is absent.

12. Variations from that form which presents typical specific lesions are determined by differences in the character and extent of the eruption. On the one hand, the lesions may be few or incomplete, as in the abortive types; on the other, they may, very early and before being visible to the naked eye, be accompanied by diffuse hemorrhages into the corium, as in purpura variolosa. In any case, forms exist intermediate between the representative type of the disease and the variation.

(b) Associated Lesions of Indeterminate Specificity.—(1) Proliferation within the hematopoietic organs is constant and well-marked, and gives rise in the spleen, lymph-nodes and bone-marrow, to the formation of mononuclear, basophilic cells, and in the nodes and marrow to phagocytic endothelial cells. The former pass into the blood in large numbers. This process, present to some degree in other infectious diseases, is here so prominent as to be well-nigh characteristic.

2. Cellular infiltration with the mononuclears just mentioned, focal and interstitial, occurs constantly in the testis, and usually in the kidneys, liver and adrenals. In the testis this infiltration, by pressure and thrombosis, causes anemic focal necrosis, which seems to be specific.

3. Focal degeneration, apparently not anemic, due to the action of toxins, is present in the blood-forming cells of the bone-marrow. The lesion is characterized by necrosis, at times with hemorrhage, and accompanied by foci of phagocytic cells. This lesion is almost pathognomonic, but devoid of parasites. Diffuse degeneration, toxic in character, is present in the liver, kidneys, adrenals and testes. In the liver cloudy swelling is more marked than in any other acute infectious disease. Otherwise, the degeneration is not to be distinguished from that due to bacterial infection.

4. Inhibition of cell differentiation by the action of toxins is evidenced in the bone-marrow in the absence of complete transformation of antecedent cells into polynuclears, and in the testis in the absence of spermatogenesis. The first-mentioned is seemingly peculiar to variola.

5. The paucity of polynuclears, alike in the specific lesions, the focal degenerations, and the bone-marrow, is so constant and pronounced as to render it a striking peculiarity.

(c) **Associated Lesions, Bacterial in Origin.**—Accompanying the lesions specific or characteristic of variola, are others due to bacterial infection through channels created by them or incidental to the lowering of resistance.

1. Acute parenchymatous degeneration of the liver, kidneys, adrenals and testes, already mentioned as associated lesions, may in part be due to the action of the toxins of pyogenic bacteria usually present in severe cases.

2. Inflammatory processes, constituting complications of varied and often of great importance, are present with a frequency dependent upon their position. Boils, erysipelas, and cellulitis are common but unimportant sequelæ. Pharyngitis and bronchopneumonia are frequent in severe cases, the latter often the cause of death. Lobar pneumonia, abscess, and gangrene of lung occasionally occur. Endocarditis, pleuritis, and empyema are relatively uncommon. Acute lymph-noditis is present in all severe cases.

Pathogenesis and Etiology.—Variola seems to be most prevalent in winter and spring. In Chicago, it usually begins late in November, and increases up to June, when it subsides. In England, the disease formerly prevailed about equally at all seasons. The mortality is highest at the height of the epidemic. Young and old are equally susceptible when unprotected by vaccination.

J. Ruhräh* states that one thing which is often overlooked in thinking of smallpox is the fact that in prevaccination days every one had the disease, and at that time it was a disease of childhood, the adult population consisting of those individuals who had survived the attack, which, Lettsom states, occurred almost invariably before the seventh year. From the description of writers of that period, almost every one was more or less pock marked and the disease was regarded as a disagreeable necessity, much in the light that we now regard measles.

Sex-incidence.—There is practically no difference in the rate of males and females.

Age-incidence.—In the series of 564 patients in the Island of Trinidad, referred to by Seheult, the youngest subject was two weeks, the oldest 89 years. 56.20 per cent. occurred in adults between 20 and 34 years, while only 12.23 per cent. occurred in children under 14. This, he adds, is exactly what one would expect in an epidemic in a community such as that in Trinidad, where the Vaccination Ordinance, strictly enforced, requires the successful vaccination of all infants before the age of three months. Again, among adults more were affected during the quinquenniad 20 to 24 than during any other; and among 21 children under five years, 12 were unvaccinated infants ranging from two weeks to four and one-half months of age. These figures, he believes, clearly indicate the rôle which vaccination played.

Four instances in which the fetus was attacked came under his observation; the earliest period was after four and one-half months of intra-uterine life. Fifty-one pregnant patients were admitted to the maternity ward after recovery from the disease. Of these eleven aborted and nine were delivered prematurely. In the abortions, eight of the fetuses showed distinct evidence of an attack of the disease, and of the premature births four, including a pair of twins, exhibited external manifestations. All of those attacked were born in the eruptive stage except one, which presented the characteristic macules on the body and a deep scar on the left cheek.

The history of the twin-case is interesting: The mother developed the initial symptoms of variola on March 23, and the rash appeared on the face three days later. She was vaccinated three days before the onset of the invasion period, and both vaccinia and variola ran their course concurrently. The vaccine vesicles were typical and the attack of variola moderately severe. On April 17, when in the desquamating stage, she was delivered prematurely at the seventh month of gestation. Both fetuses showed the eruption of variola—white macerated vesicles—sparsely scattered on the scalp, face, trunk and limbs, including the palms and soles. There was one large placental mass which was partially implanted in the lower uterine

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* Forchheimer, Therapeusis of internal diseases, ii, p. 40.

segment. Each fetus was enclosed in a separate sac of membranes. The first was stillborn, and the other died in a few minutes. In this instance the fetuses were apparently infected simultaneously (or almost so) with the mother. In the other cases there was no correspondence as regards date of disease in mother and child, although allowances were duly made for the peculiar conditions which affect the evolution of rashes in the fetus. The disease was much more advanced in the mother than the fetus. It would appear, therefore, either the incubation period is longer in the fetus than the adult or that the fetus becomes infected after the disease has reached the eruptive stage in the mother. Seheult observed that the liability of the fetus to the disease seemed to decrease directly with its age.

Of 4901 deaths from variola in Kazan (Russia), referred to by Epstein—

127 were 0 to 1 month old
721 were 1 to 6 months old
1082 were 6 to 12 months old
1579 were 1 to 3 years old
703 were 3 to 5 years old
529 were 5 to 10 years old
92 were 10 to 15 years old
38 were 15 to 20 years old
30 were 20 to 80 years old

The Causal Organism.—While this is not definitely known, it seems probable that it may be one of the Protozoa. It may also be an ultramicroscopic organism. The first author to claim that protozoa are found in variola was Grunhagen over half a century ago (1872). Some years later (1887), Van der Loeff described structures like the *Ameba.* During the next decade a series of articles appeared by Pfeiffer in which he gave an account of the *Monocystis epithelialis,* found in variola, and vaccinia as well. It is now believed the last two observers mistook fragments of epithelial cells, or of white blood cells, for protozoa.

In 1892, Guarnieri gave a description of bodies found in the pustules, which he called *Cytoryctes variolæ.* They were also met with in the cornea of rabbits after experimental inoculation. Councilman, Magrath and Brinckerhoff demonstrated that these vaccine bodies were a phase of the development of a sporozöon.

While a number of authors consider these bodies to be the cause of variola and vaccinia, and believe them to be protozoa another group of investigators during the past years (Prowazek, Foa and others) believe that the Guarnieri bodies are not protozoa. Variola and vaccinia virus is filterable while the Guarnieri bodies are not. The above mentioned investigators believe that the Guarnieri bodies surround the causative organism and that the bodies are the products of specific reaction of the diseased cell. They consist largely of plastin-like or chromatoid components. The Guarnieri bodies are of diagnostic importance, since their presence indicates variola or vaccinia.

Hammerschmidt* made some interesting observations on the nature of the Guarnieri bodies. He concludes that the causative organism of variola acts in some way on the nucleolus of the epithelial cells or the cornea and skin, producing a marked increase in the nucleolar substance. The nucleolas leaves its normal position in the nucleus and comes to lie in the plasma and leads to the formation of Guarnieri bodies. The author believes that similar conditions prevail in lyssa and dog distemper.

It is the function of the nucleolus, according to Hammerschmidt's theory, to secrete substances which will enable the epidermal cells to resist the virus for years after the disease has been overcome.

In 1917, Hallenberger made some additional observations. The bodies observed he termed strongyloplasma and believed that these organisms should be classed between the bacteria and protozoa. Numerous pyogenic organisms are contained in the pustules. Staphylococcus albus, aureus and citreus and the streptococcus pyogenes occur. They may be obtained by blood culture. It may be assumed that the symptoms during the suppurative stage of variola are not only due to the specific organism, but depend in some part upon the mixed infection with these pyogenic organisms.

Clinical Varieties.—Smallpox, like other diseases, is met with in all degrees of severity and at every age, from the mildest type that does not require the patient to remain in bed, to the formidable type from which there is no recovery. We meet cases which terminate at the end of the invasion period without eruption. Then we see patients with but one papule or two, three, four or any number. Then again, we meet cases so severe that the capillary blood-vessels give way with consequent hemorrhage into the skin and onto the mucous surfaces, invariably resulting in death of the patient.

For convenience of study, we classify smallpox into six types:

1. Variola, without eruption.
2. Discrete variola.
3. Confluent variola.
4. Pustular hemorrhagic variola.
5. Hemorrhagic variola.
6. Fetal and infantile type.

(So-called "varioloid" is described under discrete variola.) A disease which presents a sliding scale of severity from the benign to the fatal type will show different degrees of intensity of the types named, and this should always be kept in mind when making a diagnosis.

I will first describe a fairly typical case of smallpox of average severity. After an incubative period of 10 to 14 days—an average of 12 days†—the patient has a chill or a chilly feeling which may last a few hours or half a day. In place of a chill, a child may have a convulsion. Chills or convulsions are immediately followed by fever and sometimes delirium. The fever varies from 102° to 106°, usually 104°F. The pulse is strong and increased about one-third faster than normal.

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* Ztschr. f. Hygiene u. Infektionskrankheiten, lxxxix (1919), pp. 49–86.

† Wanklyn, the well-known English epidemiologist, emphasizes the "singular" constancy of the 12-day period of incubation.

The child has headache, usually frontal, backache and nausea, and sometimes vomits. There is often pain in the epigastric region. Digestive disturbances, associated with anorexia and severe diarrhea, are frequently observed. The tongue is coated with a thick yellowish or whitish fur. The breath is foul. The child is restless and wakeful because of headache, backache, and the other distressing symptoms. These symptoms will not abate, but increase in severity in some degree until the evening of the third day, or the morning of the fourth day, of the disease, when a macular eruption appears first in the throat, on the face about the mouth, chin and nose, and on the forehead. It shows early on the genitals, and last on the lower limbs. It appears in the scalp. No part of the body is exempt.

In a few hours these macules become papules. As this eruption appears on the skin, the fever and all painful symptoms such as headache and backache totally disappear and the child has a feeling of comfort and will readily get up if permitted to do so. The papules which are small and hard begin to fill with fluid and within 24 to 36 hours become vesicles. They continue to fill and enlarge as vesicles until about the fifth day of the eruption, when the contents become milky. This is the beginning of the pustular stage. During the vesicular stage, there is a flattening of the lesion, a dipping down in the center of the vesicle. (This is called "umbilication" and is usually present in the type of case here described.) The pustules continue to enlarge until the eighth or ninth day. They remain intact unless torn by scratching or broken by violence.

About the eighth day of the eruptive stage, the umbilication gives way and the lesions become spherical or conoid. About the ninth or tenth day, the pustules begin to dry and shrink on the top which causes them again to appear flattened. This is called "secondary umbilication." From about the eleventh day, the pustules dry and form scabs, the scabs forming on the face first and hands and feet last. The lesions disappear in the order of their appearance. The scaling or desiccation is usually complete by the fourteenth or eighteenth day, except on the soles of the feet and the palms of the hands. The inspissated pus and blood remains under the thick epidermis of the soles and palms for weeks if not removed by opening the pustule and cleaning out the dried blood and pus.

After the patient has desquamated, there remains a pigmentation of the skin at the site of each lesion. This pigmentation continues for months and in some instances for years. If the inflammation has been severe enough to destroy the skin, pox marks will result; otherwise, no permanent pox marks will be present. The temperature which drops to normal when the eruption appears, recurs in four or five days at the beginning of the pustular stage and continues until desquamation is well established, subsiding as the acute inflammatory condition of the skin diminishes. During the later vesicular stage and all through the pustular stage, the burning and itching are intense. The distress and misery prevent sleep. The child must lie on a skin covered with painful sores. The weight of the body even on a soft bed causes pain, and to move is torture. The throat becomes inflamed and swallowing is painful during the vesicular and pustular stages. Frequently there is an exudate on the pharynx and tonsils. The flow of saliva is increased. The lesions also occur on the mucous membrane of the nose, causing obstruction to respiration. Delirium may occur. Cardiac weakness and symptoms of collapse may be noted at this stage.

Occasionally on the first or second day an initial rash appears. Sometimes this rash resembles measles and in other cases it simulates scarlet fever. It appears on the first or second day of the fever, and fades as the papular rash develops on the third or fourth day. This initial eruption is present in one case in about 350, but it is important to recognize, as a mistaken diagnosis of scarlet fever or measles is usually made. It should be possible to recognize the nature of the disease on the fourth day as the initial rash has disappeared and the characteristic papules are present.

1. Variola Sine Eruptione.—This variety presents the initial symptoms of chill, fever, headache, backache, nausea, coated tongue and accelerated pulse. All the classical phenomena of the invasion stage may be present as in the severe form, up to the morning of the fourth day when a complete cessation of all these symptoms takes place, though no eruption can be found. In an unvaccinated patient with a known exposure to smallpox a presumptive diagnosis may be made. This is especially true when several individuals have been exposed to the infected patient simultaneously. Some present an eruption, while others are free, though the symptoms are identical in all the cases up to the eruptive stage.

2. Discrete Type.—Under the discrete type are classed all cases of mild smallpox. The so-called "varioloid" is smallpox modified by a vaccination which by age has lost some of its protective influence. The initial fever may be as severe as in the confluent type. The temperature in the mild type of smallpox always drops to normal when the eruption appears. The life history of the lesions is the same as in the typical case. If no pustulation occurs, secondary fever is absent.

Alastrim.—Mild forms of smallpox have received different names in various countries. Thus, varioloid is probably similar to alastrim in Egypt, the Soudan, and the West Indies. Similar mild forms in Brazil are substantially identical with the South African Amaas and Kaffir milk-pox. These conditions, variously named, are undoubtedly a form of smallpox originally mild in character and with a low mortality rate. Under conditions which are unknown, these mild forms are capable of taking on virulent character and causing severe disfiguring and highly fatal type of smallpox.

Recent successful vaccination protects against these milder forms. In an epidemic of alastrim in Jamaica, 1920, described by MacCallum and Moody, the mortality was very low. The children who contracted the disease shortly after birth died within the first month of life. Two macerated fetuses were born a month after the mother had an attack of alastrim. They appeared to have pock marks on the skin. The prognosis in this epidemic was reported to be favorable, except that in the hemorrhagic type and in the newly born infants the mortality was high and, as has already been stated, fetal alastrim was relatively frequent. On the other hand, many of the older infants and children show a tendency to a mild type of the disease.

3. **Confluent Type.**—In this form the various symptoms mentioned in the typical case are intensified. The initial temperature may reach the same level, and sloughing and necrosis, with the formation of abscesses, occur more frequently. Occasionally the fever does not drop when the eruption appears, but continues through the various stages of the disease.

4. **The pustular hemorrhagic variety** runs the same course as the typical case described, except that hemorrhages into the pustules take place. Under all circumstances this is known to be a very grave form of variola. Death may occur on the seventh to the ninth day, though in some instances takes place on the third or fourth day.

If the hemorrhage into the pustules takes place early in the disease, the chance for survival is slight. On the other hand, if these hemorrhagic pustules continue, permitting a complete efflorescence of the pustular stage, the prognosis is a little more favorable.

5. **Hemorrhagic variola** resembles the other types during the invasion period, but on the second to the fourth day the papular rash does not appear. A diffuse hyperemic rash frequently appears, being noted especially in the groins. These are usually petechial spots. Ecchymoses frequently take place into the conjunctivæ and hemorrhage from the mucous membranes may occur. In a short time the skin contains numerous purpuric spots, many of which have coalesced. The face becomes edematous and the body assumes a purplish hue. These cases usually terminate in death in three or four days, though in some instances death occurs before the purpura is fully developed. (Sometimes an "abortive" type is noted.) The lesions become vesicular and the contents are absorbed, but no pus forms.

6. **Fetal and Infantile Variety.**—Some years ago Epstein gave the details of an infantile patient with variola who was born June 26, 1912, at full term. The mother developed a generalized hyperemia June 27, and variola June 28. She died July 7. The infant was vaccinated June 29. It began to vomit on the next day; developed diarrhea July 1, a macular rash in the inguinal region July 2; a papulovesicular eruption, vomiting and diarrhea. This eruption became confluent July 5, and vesicles and pustules continued to develop

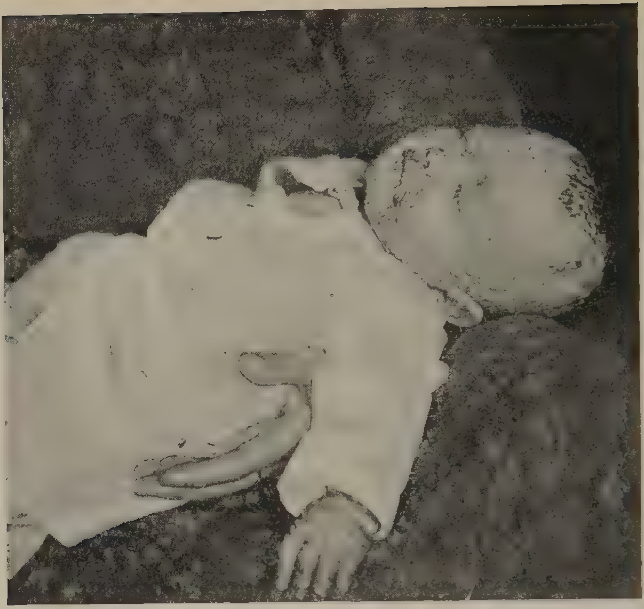

Fig. 14.—This child, 18 months old, died from confluent smallpox eighth day of the eruption, eleventh day of the disease. *Never vaccinated!*

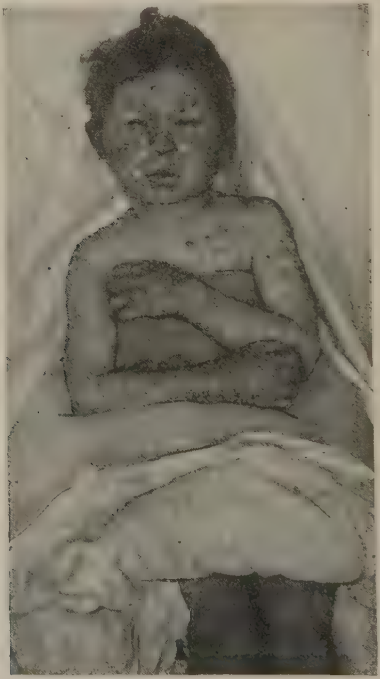

Fig. 15.—A severe, discrete smallpox in a child seven years old. Eighth day of eruption, eleventh day of the disease. *Never vaccinated!*

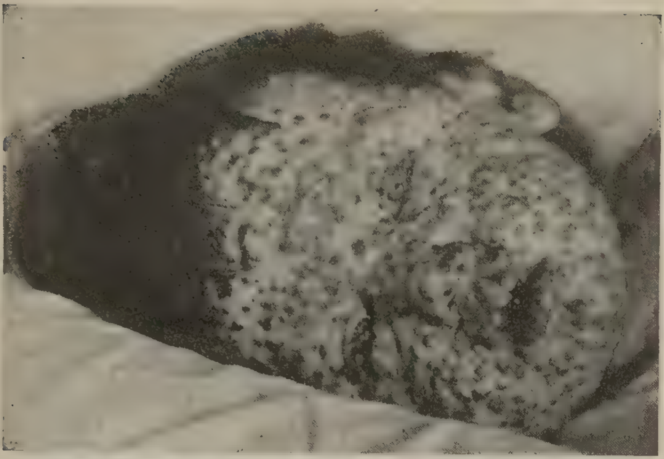

Fig. 16.—Child three years old. Died from semi-confluent smallpox on ninth day of the eruption, twelfth day of the disease. *Never vaccinated!*

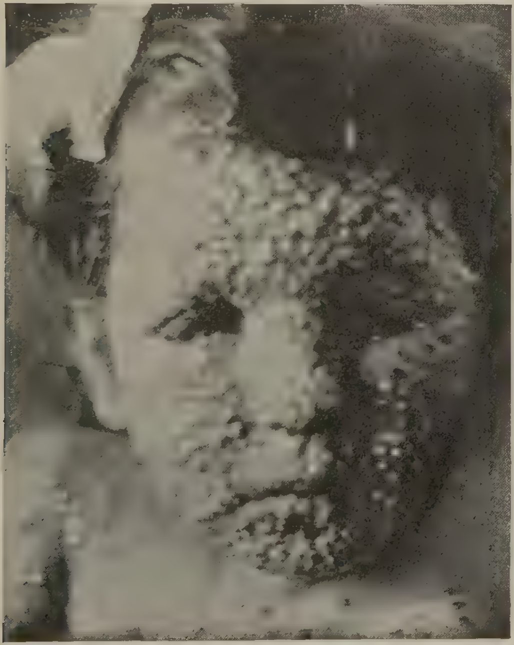

Fig. 17.—Child five years old. Confluent smallpox on the face eighth day of eruption, eleventh day of disease. *Never vaccinated!*

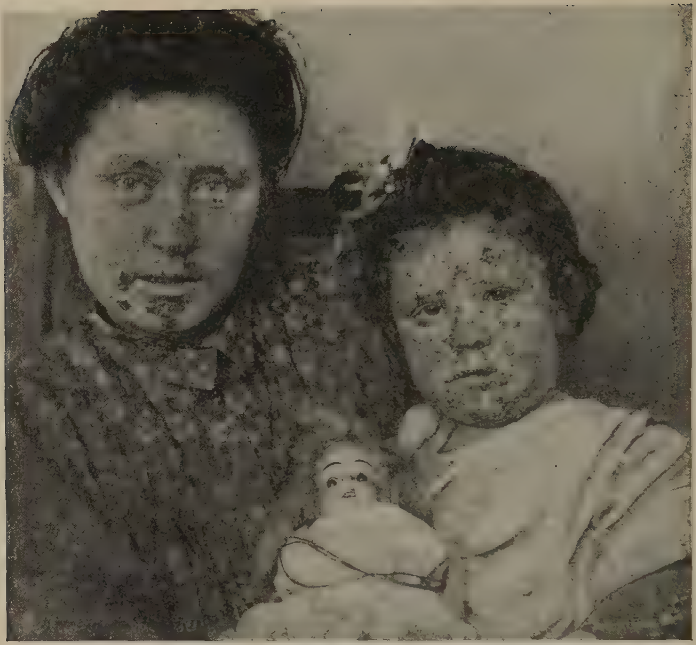

Fig. 18.—Discrete smallpox. Sixth day of eruption, ninth day of the disease. *Never vaccinated!* The unvaccinated mother is just recovering from severe, discrete smallpox.

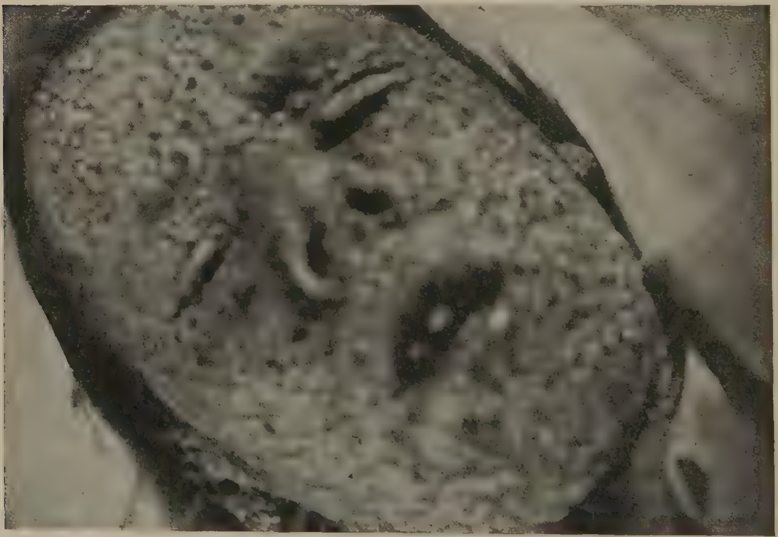

Fig. 19.—Child nine years old. Died from confluent smallpox. Ninth day of the eruption, twelfth day of the disease. *Never vaccinated!*

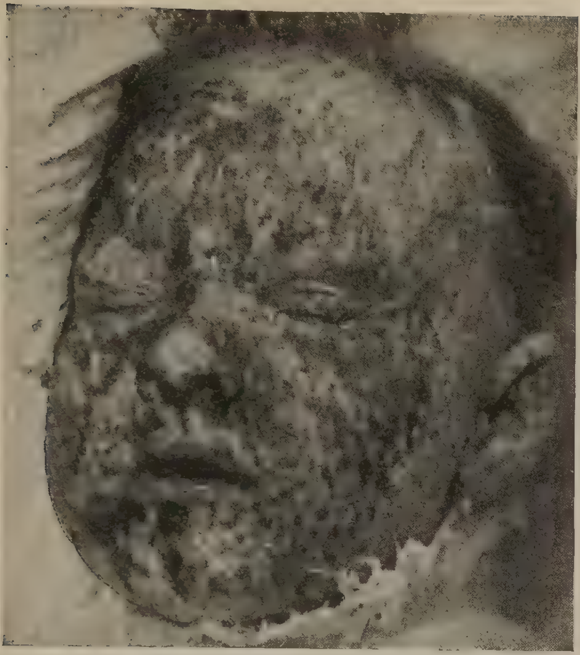

FIG. 20.—Child three years old. Died from confluent smallpox. Tenth day of the eruption, thirteenth day of the disease. *Never vaccinated!*

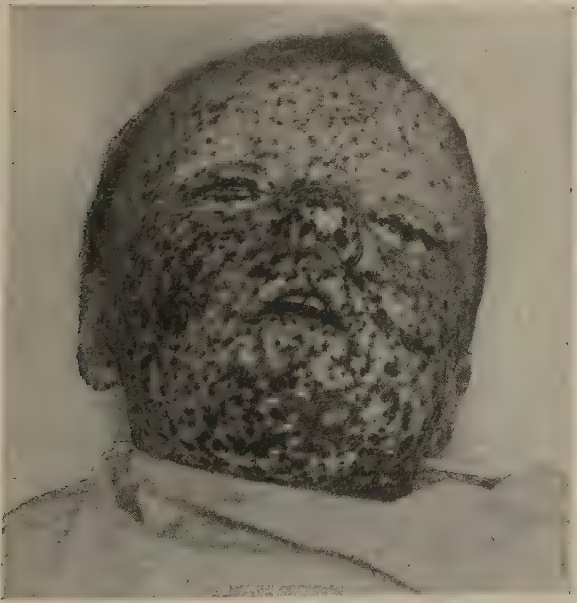

FIG. 21.—Child three years old. Died from confluent smallpox. Eighth day of eruption, eleventh day of the disease. *Never vaccinated!*

on the following day. July 7 the vaccination became pustular. The general condition grew worse, and death ensued on July 9. The anatomic diagnosis was: Variola, with profuse eruption of skin and mouth cavity, fatty degeneration of the heart-muscle and liver; degeneration of the kidneys; splenic tumor; edema of the brain; hyperemia and atelectasis of the lungs; catarrhal bronchitis and acute rhinitis.

The temperature curve showed a rapid rise with slight morning remissions in the initial stage; a drop to normal with relative euphoria after completion of the primary eruption, and another rapid rise with the beginning of the purulent stage. The pustules were similar in size to those of adults, but were flatter and not so high. They were more of the shape of wheals, and many were not indented. Unilocular vesicles were present on the palms and fingers, and on the perineum- The lifting-up of the epithelium through vesicle formation by copious collections of fluid in the necrotizing tissue, seems to be more frequent during the florid stage in the newborn and in young infants.

From the etiologic standpoint this case is especially interesting because it raises the question of placental transmission. The occurrence of the variola on the eighth to ninth day which was met with in five cases by Epstein, has also been observed by Bednar. It is believed that the infants were infected during labor, or later by contact, a shortened period of incubation being assumed. However, infection during intra-uterine life is not excluded.

The following groups of placental infection are distinguished:*

1. Mother is Healthy, the Ovum Infected.—It is recorded of Mauriceau, the famous obstetrician, that he was born with six variolar pustules; his mother never having suffered with the disease, but a brother died of variola on the day previous to his birth. (The diagnosis has been questioned by several authors.)

There are undoubted cases in the literature. In all instances the mother had been exposed to variola. In the two observations of Jenner, the mothers had been vaccinated, had been in close contact with variola, and gave birth to infants with variola. Such cases are explained by Pfeiffer on the assumption that the variola did not develop in the immune tissues of the mothers, but that any germ which might have reached the blood of the ovum multiplied there. On the other hand, Curschmann believes that in these cases a *variola sine exanthemata* may be present in the mother. He reports the case of a 40-year old mother who during the eighth month of pregnancy became ill with symptoms indicating the onset of variola. But on the fourth day the fever subsided, and there was no trace of the expected eruption. On the tenth day of illness she gave birth to a child which was covered with a variolous rash, and died three days later in the suppurative stage.

Laurent has collected more recent examples. He himself, in 1884, demonstrated a macerated fetus with umbilicated pustules. The anatomic diagnosis was variola. The mother had been vaccinated in childhood, and was in good health four weeks previously. Franklin observed the case of a full-term stillborn infant with typical variolous pustules. The mother had no sign of the disease, but the father had had an attack of variola about four weeks before the birth of the infant.

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* For the description of variola in newborn and young infants the author is indebted to the description of Alois Epstein, Arch. f. Kinderh., lx–lxi.

2. Variola during Pregnancy.—*Abortion.*—The fetus may die because of the mother's illness, and be aborted before there are any signs of variola. Women who become ill early in pregnancy, usually abort early also. It is uncertain whether the death of the fetus is due to the infection or to the general reaction. Meyer believes the fetus is less susceptible to variola than the newborn and very young child.

3. Variola during Pregnancy.—*Variola of the Fetus.*—The fetus from a woman with variola may be born intact. The conditions under which the virus will or will not be transmitted to the fetal circulation are not known. It is probable that hemorrhages of the placenta favor the transmission.

The behavior of twins under these conditions is of special interest. They may both be infected (as in the case seen by Pechmann), or one may be infected and the other remain free. In some of these instances there were two amniotic sacs and two umbilical cords. Chautreuil, Madge, Huc, Kaltenbach—each mention sets of triplets in which but two of the three were born with variola.

Reports are made from time to time, *e.g.*, by Grätzer, of children born with pock marks. Epstein states he has seen several examples of scars in the newborn, but these were not due to variola. The one under the observation of Lynn seems the most convincing: This concerned a woman who fell ill with variola during the eighth month of pregnancy. Twenty-eight days later she gave birth to a child covered with the eruption. Inoculations made from the child resulted in typical variola. Bouchut observed fetal smallpox eight times. Curschmann believes this to be rare, and reports a case with variola in the fifth month of pregnancy. In the more recent literature fewer examples of fetal smallpox are met with, and it is considered rare.

4. Variola of the Mother during the End of Pregnancy: Apparently Healthy Infants Which Later Develop Variola.—Such cases are the most frequent. They are seen in asylums connected with maternity hospitals. Examples have been placed on record by Bednar, von Ritter and Epstein, among others. Curschmann found that none of the children born in the smallpox wards remained free, although some had merely a slight eruption. Cowie and Forbes give details of three cases of this type; Taconnet, one; Korybut-Daskiewicz, one; and Mayringer, four.

The child apparently healthy, becomes ill soon after birth. It may succumb to the infection before the appearance of the eruption, or may develop manifest variola to which it succumbs almost invariably. The eruption may appear during the first days of life. In such instances there is no doubt that the infection occurred *in utero* by way of the circulation, through the infected amniotic fluid. As a rule, the eruption commences on the seventh to the ninth day. Here infection is probably by contact.

Complications and Sequelæ.—It would be expected that a disease which is characterized by numerous small foci of pus in the skin would be complicated by pyenic manifestations. That this is true is shown by the fact that minute abscesses may be found in all the tissues and organs. Lymphangitis and erysipelas are sometimes observed. Furunculosis is not an infrequent complication. Abscesses in the skin—superficial as a rule—frequently occur. They are of varying size, and may be very numerous up to forty, fifty or more. While they may occur in any part of the body, the scalp and the extremities are the sites of predilection. Occasionally bedsores develop, and even gangrene. Sometimes larger abscesses occur in the deeper layer of the skin.

The regional lymph-nodes may become infected and break down, forming abscesses of considerable size.

The eruption not only occurs on the skin, but frequently involves the mucous surfaces, producing the so-called exanthem. The eruption frequently appears in the larynx and trachea and on the bronchi. In severe cases pustular and necrotic processes of the mucous membranes of the larynx and death frequently result. Bronchopneumonic foci with production of abscess and gangrene are not uncommon complications.

Severe parenchymatous and fatty degeneration of the heart muscle is of frequent occurrence and is observed as an autopsy finding in all severe cases. Vegetative endocarditis is not often observed.

Nephritis is not unusual. Albuminuria is common, especially in the early stages. Purulent effusion into the joints has been reported, though it is not a common complication. The autopsy frequently reveals an encephalitis manifesting itself as small foci of inflammation in various parts of the brain. Inflammatory areas in the spinal cord, producing paraplegia and other forms of myelitis, have also been observed.

Paralysis of the peripheral nerves occurs in those areas where there is exudate and necrosis. This is not true in the palate and pharynx. As the patient improves, he tends to recover from these paralytic symptoms. Suppurative otitis media, with all its complications, may occur. Keratitis, perforation of the cornea, iritis and pan-ophthalmitis may occur in the severe cases. In the hemorrhagic cases, hemorrhages into the conjunctiva and also into the retina have been observed.

W. L. and C. B. Brown have quite recently called attention to osteomyelitis variolosa, reporting two cases. This is comparatively infrequent. It was not present in 390 cases at El Paso, Texas, in the previous eight years. There seem to be two forms: (*a*) The ordinary pyogenic metastatic form; and (*b*) a distinct necrosing non-suppurative one, probably due to the specific virus, and most frequent in children.

Necrotic changes in the bone-marrow have been noted by Chiari during the eruptive period. Some authors have attributed the characteristic severe lumbar pains to these changes.

Diagnosis.—The diagnosis of variola is readily made when a well developed, pustular eruption is present. Recognition of the disease is more difficult in discrete variola, since there are various atypical forms. The diagnosis is most difficult during the initial stage and at the onset of the eruption. It is essential to recognize the condition at this stage since the spread of the disease may be prevented.

On the first day of the initial stage, it is impossible to make a positive diagnosis. The sudden rise of temperature, the chills, marked backache and disturbed sensorium point to a severe infection. Influenza, pneumonia, typhus, malaria are thought of, rather than smallpox, especially in regions where this disease is uncommon. If the patient has been exposed and especially if he has not been vaccinated recently, smallpox should be considered, especially if severe backache is a prominent symptom.

Claude Buchanan Ker, commenting on this difficulty, says that all the symptoms occurring in the initial period of smallpox may be present in influenza: Backache in particular, which is present in both. When both fevers are epidemic, it is practically impossible to arrive at a diagnosis unless a petechial rash is present. In the majority of cases it will be necessary to wait until the smallpox papules begin to appear before a definite decision can be reached. If no eruption appears by the fourth day, it should be fairly safe to conclude in favor of influenza.

The appearance of the initial eruption in smallpox is highly important from the diagnostic standpoint. The hemorrhagic type, characterized by petechiæ distributed especially in the groin and cubital spaces, occurs comparatively rarely and only in the more severe types. It develops rarely and should therefore lead to correct diagnosis on the first day. The eruption may be mistaken for hemorrhagic scarlet fever, but the history of exposure and of the typical symptoms, especially the backache, aid in the diagnosis.

The second type of prodromal rash is the erythematous roseate form which must be differentiated from scarlet fever and measles. In the latter, catarrhal symptoms are marked. The presence of Koplik spots and the temperature curve are further aids in diagnosis. While in the prodromal period of measles the temperature on the first day rises to 100.5 or 102.5°F., falls on the second day and rises again when the eruption appears, in smallpox the temperature falls with the appearance of the rash. In scarlet fever the temperature reaches its maximum with the appearance of the eruption and remains high for a period of time. The eruption of purpura hemorrhagica, drug rashes, urticaria, from shell fish, iodides and bromides must also be considered in the differential diagnosis of the prodromal rash.

In the eruptive period of smallpox, when the specific maculopapules first appear, measles, typhus and typhoid must be considered. The prodromal period of measles and smallpox are equally long. The smallpox rash is papular at first and therefore can hardly be distinguished from a beginning measles eruption.

A group-like arrangement of the rash speaks for measles, an irregular distribution for smallpox. Study of the temperature curve is the most valuable aid at this stage. A markedly positive Diazo reaction speaks for measles.

The blood picture is of aid in the differential diagnosis. In the beginning stage, a large number of mononuclear leukocytes is characteristic, for smallpox. When the disease is well developed, there is moderate leukocytosis, lymphocytosis, normal or slightly increased number of neutrophiles. In scarlet fever the increase of polymorphonuclear leukocytes and the eosinophilia speak against smallpox. Measles is characterized by leukopenia, small number of lymphocytes, and absence of eosinophiles.

Typhus in the first three days of the disease can hardly be differentiated from smallpox, especially if there is backache. The roseolous eruption which develops on the fourth day of typhus resembles that of smallpox and the disease must be differentiated by the temperature course. Smallpox is the only acute eruptive disease which shows the characteristic fall in fever when the eruption appears.

Other acute infectious diseases which must be differentiated from smallpox in the initial stage are influenza, pneumonia, cerebrospinal meningitis, relapsing fever.

In the suppurative stage, the diagnosis is readily made in typical variola. The eruption of varicella may cause difficulty. The essential points in differentiation are: The varicella vesicles develop within 24 hours directly from roseolous eruption without the formation of nodules. As a rule, they are not umbilicated. Their contents are clear or slightly cloudy. The duration of the individual vesicles is short. They rupture after a few days and yellowish brown crusts appear. New crops of vesicles develop, so that all forms of the eruption are present at the same time. Occasionally atypical varieties of varicella occur which closely resemble smallpox. The vesicles are umbilicated and contain pus. The typical prodromal stage of variola, which is absent in varicella, aids in the diagnosis.

The distribution of the eruption is another important point in differentiation. In smallpox the eruption breaks out on the hands and feet. The involvement of palms and soles is characteristic. The face is attacked most. In varicella, the trunk and extremities are affected most.

Other pustular eruptions which must be differentiated from smallpox are syphilitides, acne, impetigo contagiosa, erythema multiforme, herpes, pustular eruptions in septic diseases, and the straw itch described by Schamberg.

Impetigo contagiosa occurs chiefly in children as a vesicular eruption which rapidly enlarges into blebs the size of a split pea to that of a five-cent piece. They appear in groups without previous symptoms.

The vesicles may become umbilicated and coalesce, and crusts form in a few days. This disease is found most commonly about the mouth, chin and hands.

Straw itch is described by Schamberg. It is due to a mite in straw, attacking laborers, but also those who sleep on mattresses made from this straw. Eruption consists of wheals surmounted by vesicles and contents ultimately become turbid and pustular. Lesions are most abundant on the trunk and are slight on the face and extremities.

Prognosis.—The mortality of smallpox in infancy and childhood depends on the number of pustules and the danger is in direct proportion to the number of lesions on the face and hands. The mortality is high in infants and young children. As has already been stated, the hemorrhagic variety is almost invariably fatal. Death often results from complicating disorders, such as pharyngitis, laryngitis, bronchitis and pneumonia. In the discrete form, the course may be very mild. In the confluent form the course is usually severe and frequently unfavorable. Children who are unvaccinated are susceptible to the disease, and are likely to contract the severe forms. Disfigurement of the face from pitting may occur in the severe varieties and cannot be avoided by any form of treatment. Blindness may occur as the result of keratitis.

The death-rate from variola in general has, of course, been greatly reduced as a result of vaccination. For example, in England and Wales, the deaths in five successive decades have (according to McVail) been as follows:

	Deaths
1867–1876	58,614
1877–1886	18,026
1887–1896	4,892
1897–1906	4,763
1907–1916	139

On the other hand, vaccination has led to a marked change in the age-incidence of the fatal cases. This is shown by the table for Berlin furnished by Gins.

	1758–74	1870–72	1914–17
Over 40 years, per cent	0.07	23.85	90.56
12 to 39 years, per cent	1.25	27.13	7.32
Under 12 years, per cent	98.7	49.02	2.12

The percentage in England is nearly as high. In the eighteenth and nineteenth centuries, 90 per cent. were in children under five, and nearly all the remainder occurred between five and 10 years (Hanna).

Among unvaccinated children, variola is always of a very severe type of the mortality ranging from 50 to 70 per cent. According to Hanna children under the age of two years, seldom recover when the eruption is confluent, while those between five and 10 years have a lower mortality than those under five.

The influence of vaccination is shown in the following tables from this author:

TWO HUNDRED AND FIFTEEN CASES OF VARIOLA, UNDER 15 YEARS, ARRANGED ACCORDING TO AGE-PERIOD AND SEVERITY

(This table compares the number of vaccinated with the unvaccinated children who were affected and the variety of the disease)

	Under 2		2 to 5 years		5 to 10 years		10 to 15 years	
	Vac.	Unvac.	Vac.	Unvac.	Vac.	Unvac.	Vac.	Unvac.
(*A*) Modified discrete and discrete....	0	3	7	3	31	6	54	9
(*B*) Profuse discrete and semiconfluent........................	0	9	0	15	3	15	8	19
(*C*) Confluent and death............	0	17	0	8	0	5	0	3
Total............................	0	29	7	26	34	26	62	31
Deaths alone.....................	0	17	0	8	0	5	0	1

The same group (215 cases) showing severity of disease stated in per cent.

	Under 2		2 to 5 years		5 to 10 years		10 to 15 years	
	Vac.	Unvac.	Vac.	Unvac.	Vac.	Unvac.	Vac.	Unvac.
(*A*) Modified discrete and discrete, per cent.....................	0	10.3	100	11.5	91	23	87	29.0
(*B*) Profuse discrete and semiconfluent, per cent...............	0	31.0	0	57.0	9	57	13	61.5
(*C*) Confluent and death, per cent....	0	58.0	0	30.6	0	19	0	9.7

Treatment.—Prophylaxis Vaccination.—The treatment for smallpox properly begins with prophylaxis. If all babies were vaccinated before three months of age, or even before the sixth month, it would not be necessary to write a chapter on the treatment of smallpox in children. During the first three months is the best time to vaccinate. Babies are less liable to secondary infection and there is less reaction to the vaccine than is the case later on.

A vaccination to be protective should show a life history similar to a smallpox lesion. It is characterized by a vesicle which in turn becomes a pustule with a circumscribed and mild inflammatory area, accompanied by a febrile reaction. In about 18 or 20 days, the resulting scab comes off, leaving a scar which is typical. Such a result can be obtained by using potent glycerinized lymph and is protective against smallpox for about ten years. Occasionally the protective influence is partly lost in less time, but more frequently such a vaccination will protect longer than 10 years. In a considerable number of instances a single vaccination protects for a life-time.

Retrial.—A retrial should be made in from seven to 10 years, and repeated at the same intervals thereafter. If it fails to "take," there is no inconvenience, and if it does "take," it shows that the former vaccination has—at the time of retrial—lost part of its protective influence.

No Insusceptibility.—All who have not had smallpox are susceptible to vaccinia at least once. To this rule there is probably no exception. In an extensive experience, I have never met with one.

The operation should be repeated until a successful result is obtained. To say a person is "insusceptible to vaccinia" because several trials are negative is unjustifiable. I have known several to lose their lives because physicians had given this false information.

Technique of Vaccination.—The vaccination should be performed with the same care that is used in any surgical operation. (This statement is made for the few who still think a vaccination needs less attention than other skin lesions.)

A baby can be vaccinated on the arm or leg. If a boy, vaccinate on the arm at the insertion of the deltoid. If a girl, vaccinate high on the arm near the shoulder, or on the calf of the leg. As the child does not walk about, the leg can be selected with safety, if the vaccination is protected from contact with the body discharges.

First, sterilize the site of vaccination. This can be done with soap and water, followed with alcohol on sterile cotton; allow a little time for the alcohol to evaporate.

Second, express a drop of vaccine onto the sterilized skin with a rubber bulb.

With the vaccine in place on the skin, there are five methods of introducing it which have proved satisfactory:

1. *A single prick* through the vaccine into the skin with a needle will give good results. The resulting sore will be small, but pricking through the skin hurts the child.

2. With a dull sterile needle, make a single scratch through the drop of vaccine on the skin. Make a scratch *no more than one-eighth of an inch* long. A half-inch scratch makes too large a sore.

3. Insert the needle *between* the layers of the skin, beneath the drop of vaccine, from several directions, being careful not to go through the skin. With the left hand, grasp the arm and make the skin tense. Hold the needle parallel to the surface as in making the Schick test, so as to avoid going through the skin. The injected surface should not be larger than one-eighth of an inch in diameter.

4. Pass a dull needle through the drop of vaccine and irritate and abrade until red a surface not larger than *one-sixteenth* of an inch in diameter. Avoid bringing blood. Dress with sterile gauze. Avoid shields unless used temporarily while the vaccine lymph is drying.

5. The intracutaneous injection of pure vaccine has been practiced with good results. It avoids the scar and if aseptically performed is safe. The absence of a scar makes it difficult to prove vaccination later if desired.

Make but one mark. Vaccinia is a systemic disease and one point of insertion is as protective as many, unless there is an interval of time between vaccinations. As soon as the diagnosis of smallpox has been made, the patient should be securely isolated in a special hospital designed for this purpose. All persons who have been exposed to the infection should be vaccinated.

Medical Treatment.—The treatment of smallpox is best discussed as it is applied to the disease at different stages of development—the incubative, the invading, the eruptive, the desquamative and convalescent stages:

Incubative Stage.—After the reception of the infection of smallpox, nothing is known to be of any service in preventing the disease except vaccination, and this is not effective unless applied during the *first three days* after the infection has taken place. The action of vaccine inoculated hypodermically is quicker than smallpox infection acquired in the usual way. Anyone exposed to smallpox should be vaccinated each day for three days after such exposure. This method may result in three active vaccinations, but it is safer than to make one vaccination and wait for results. By the time we are able to tell the results of a vaccination, the period of three days is passed, and the chance for staying the disease lost if the trial is a failure.

If vaccination has not been applied soon enough to prevent the disease, an attack of smallpox is almost inevitable.

Invasion Stage.—This stage lasts three days—exceptionally two or four days. It should be the aim at this period to palliate distressing conditions and promote comfort. For lowering excessive temperature, cool sponge baths should be applied and ice to the head if there is severe headache. Convulsions at this stage are best treated by hot baths and, if persistent, chloral by mouth or by rectum. A liquid diet should be given with an abundance of water.

All the painful symptoms become more severe as the disease approaches the eruptive stage. The fever often reaches 106°F., severe backache, intense headache, nausea, anorexia and sometimes delirium. For delirium (and the other principal symptoms just named) a sponge bath or a tub bath of cool or tepid water is better than drugs in the treatment of children. The evening of the third or the morning of the fourth day, the eruption on the skin appears and all the distressing symptoms cease as a rule. Headache, backache, nausea and fever disappear. Sometimes the fever persists for a day after the eruption appears; exceptionally the fever remains throughout the course of the disease.

The Eruptive Stage.—When the eruption appears, there is a feeling of well-being for a few days and little or no treatment is needed. The patient feels well. At this time, the appetite is usually good and the child can take milk and other foods, suitable to the age, freely: Such as custard, poached or boiled eggs, milk toast, oatmeal and cream, rice and baked apple. The mild discrete cases have no secondary fever, and can eat in moderation such food as the child is accustomed to in health.

About the second day of the eruption, the papules become vesicular and continue to grow and fill with serum until about the fifth day, when the contents of the vesicles turn white or milky in color. This is the end of the vesicular and beginning of the pustular period. As a rule, the fever which disappears as the eruption comes out does not return until the beginning of the pustular period. The treatment during the papular and vesicular period, aside from feeding, is to be directed principally to the mouth and throat. The vesicles in the mouth and throat covered with the thin mucous membrane rupture early and leave superficial, painful ulcers. This treatment is important as the patient can and will take nourishment better. Without such treatment, it is sometimes difficult to induce patients to take nourishment enough, as the act of swallowing is so painful. Direct the patient to wash the mouth and throat with any antiseptic wash. An atomizer may be used to spray the solution into the pharynx.

Conjunctivitis is frequently present and is due to one or more vesicles located on the inner surface of the eyelid. These vesicles should not be opened as the rough edges of the ulcer irritate the conjunctiva more than does the unbroken vesicle. Instillation of boric acid solution, protoargol 2 per cent., argyrol 2–5 per cent., or vaseline, mercurochrome or yellow oxide of mercury ointment may be applied in the usual manner. Perforation and destruction of sight from deep ulceration sometimes result.

All attempts in the early period to avert pustulation have been futile. Nevertheless, treatment with permanganate solution has recently been recommended. The local application of a solution of potassium permanganate was first recommended by Dreyer, of Cairo, in 1910. The whole body is painted over with a freshly prepared saturated solution of potassium permanganate. Depending on the sensitiveness of the skin, the same solution, or a 1½ per cent. solution, is used. In children weaker solutions may be used. It is claimed that this treatment prevents complications, septic fever, extensive bed sores, purulent metastases, and general sepsis and shortens convalescence. Lastly, owing to the prevention of severe suppuration, smaller scars may be expected.

None of the numerous remedies recommended for internal administration with a view to aborting lesions has, in our experience, modified in any degree the course of the vesicle. All kinds of applications to the skin have been useless in lessening the destruction of tissue.

We have applied dressings which excluded the actinic rays from the lesions without any beneficial results. We used the Finsen red light treatment extensively; it was worse than useless. Patients, while in delirium, imagine the house is on fire and in one instance plunged through a window to escape. The various local applications resorted to during the pustular period seldom give relief. Where there is intense itching and discomfort, application of ice cold water seems to give the most relief. The use of appropriate stimulants may be applied in threatened heart weakness. In septic cases, and during the suppurative stage, the use of alcohol has been advised. Opiates at times are required for pain, restlessness and discomfort.

Children do not take opiates with the same degree of safety as adults, but a dose of morphin in proportion to the age of the child, or camphorated tincture of opium can be used with the same beneficial results in allaying distress and inducing sleep as for adults. Sometimes at this period there is little or no appetite. The throat is sore and swallowing painful, which causes a child to reject food. The child should be urged to take nourishment: Milk, either warm or cold, and ice cream. If milk is not well borne, buttermilk or whole lactic acid milk may be employed. Rectal alimentation may be necessary.

The condition during the pustular period calls for supporting treatment:

1. Allay pain and combat exhaustion.
2. Do nothing that will prevent natural desiccation.
3. Combat toxemia.
4. Conserve the patient's strength in every way possible.
5. Treat complications as such conditions indicate.

The inflammatory condition about the pustules causes great pain and distress. The fever, itching and burning sensations and often delirium cause sleeplessness, and rapidly exhaust the strength. Bromids and chloral may be given to induce sleep, but these drugs are not well borne and are not very efficient. The actively painful and distressing condition of the skin is usually present from the sixth day of the eruption to the ninth, or a day or two longer in severe cases. The greatest mortality from smallpox occurs from the seventh to the tenth day.

Stage of Desiccation.—As the pustules dry, forming scabs, the acute inflammation of the skin subsides. At this time, baths, antiseptic ointments and powders may be used with benefit. Frequent warm baths clean the body, soften the scabs, and hasten desquamation. Oxide of zinc ointment may be used to relieve distressing skin symptoms. In the latter pustular period and in the desquamative period, the sheets upon which the child lies should be sprinkled with a dusting powder. The sores stick to the sheets and when the latter are removed, tear the skin and produce pain. The sheets must be changed four or five times daily, and kept sprinkled with the dusting powder.

Patients should be cautioned not to scratch the lesions. In young infants it may be necessary to restrain the use of the arms and hands by the use of light splints. When pustules coalesce to form large blebs, they should be opened. Frequent lukewarm baths to which bran has been added are recommended for the severe itching during the drying of the pustules. Powdering with salicylic powder may also be beneficial. In order to prevent the child from tearing off the scabs, ointment may be employed or the arms may be held with cuffs or splints. Furuncles, discharging abscesses, impetigo, erysipelas or gangrene should be treated symptomatically. The same is true of complicating pneumonia, bronchitis, laryngitis, pleurisy or nephritis.

Convalescent Period.—Keep the patient clean by frequent baths. Treat boils and abscesses in the usual way. During this period the patients may have a liberal diet. The usual rules of hygiene should be applied. Children should have fresh air and sunlight. The inspissated blood and pus which are retained under the thick epidermis on the soles of the feet and the palms of the hands may be evacuated by incision. This avoids a prolonged quarantine. A patient can be permitted his liberty as soon as the scaling is complete and the skin smooth. A mild case may be non-infectious after three weeks. Severe cases may be the source of infection six or seven or even eight weeks.

Recapitulation.—(1) Vaccination with revaccination is an absolute preventive of smallpox.

2. There are no remedies that have any specific curative influence over smallpox.

3. The treatment is limited to palliation, the use of supporting remedies, especially food, and vigilant, intelligent nursing.

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CHAPTER CXLV

VACCINATION

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Vaccination is the inoculation with the virus of vaccinia or cowpox. It produces an acute specific disease, which follows a definite course, usually with few constitutional symptoms, and confers an immunity against smallpox for a varying period.

History.—It is hard for us in this day and generation, when most of the medical profession have seen only a few cases of small-pox and some, none at all, to appreciate the frightful ravages this disease made in civilized and uncivilized countries in olden times. At times in some countries half the deaths were due to small-pox. It was once the most prevalent and destructive disease that ever scourged mankind. If we compare the small-pox epidemics of olden times with present-day epidemics of measles, whooping-cough and chicken-pox, we obtain some slight notion of its prevalence. It existed continuously endemically, and every few years epidemically, spreading through all avenues of intercourse and trade and attacking people of all classes, conditions and ages. The disease was so common and so general that it was quite exceptional for anyone living in a populous district to reach adult age without having contracted it. In fact an old proverb, maintained that "From love and small-pox, none remain free."

In the sixteenth century it destroyed 3,500,000 of Mexico's inhabitants. During the same century it exterminated whole races of men in Brazil. It nearly depopulated Greenland and Iceland. Of the 12,000,000 deaths occurring among the North American Indians, 6,000,000 were due to small-pox. Macaulay speaks of it as being at that time "the most terrible minister of death." Where the plague killed one, small-pox killed 100, because the plague appeared not much oftener than once in a generation. In Europe, during pre-vaccinal times, the disease annually claimed nearly one-half million victims, the great majority of which were children.

The origin of cowpox is still uncertain, and the period when it was first noticed has not been recorded. It was supposed to arise from a disease of the horse's hoof, called "grease," which Jenner described as "an inflammation and swelling in the heel, from which arises matter possessing properties of a very peculiar kind." The person who took care of the horse, suffering from the "grease," infected the udder of the cow with his hands. The dairy maid, in turn, became infected from the cow, and spread the infection through the herd, "until most of the cattle and domestics felt its unpleasant consequences." This rapid spreading of the disease through the herds of cows gave to it the name of cowpox or vaccinia, from vaca the cow.

"The active quality of the virus, from the horse's heels," according to Jenner, "is greatly increased after it has acted on the nipples of the cow, as it rarely happens that the horse affects its dresser, and as rarely that a milk maid escapes the infection, when she milks the infected cow." Where men attended to horses, and women to milking, as was the practice in Ireland at that time, no case of cowpox was known. This fact made Jenner feel that the "grease" might be the cause of the disease. He further felt that "cowpox is not a separate disease, but arises from an infection of the cow with the virus of animal pox or of small-pox."

Jenner has presented us with one of the very early evidences of attenuation of the virulence of germs through transmission. He stated, that when the virus was transferred to the cow for the first time, small-pox "may be produced in man from the contents of the vesicles or pustules; but after two or three transfers the virus becomes attenuated, until it is no longer so virulent. It is then not possible to produce small-pox in man by inoculating him with this virus, which has been altered by attenuation or transmission."

Though the "grease" was supposed by the farmers to be the cause of cowpox, Jenner, after a period of investigation covering over 20 years, expressed grave doubts, of its being in any way related to vaccinia. He said, "we have seen that the virus from the horse, when it proves infectious to the human subject, is not to be relied upon as rendering the system secure from variolus infection, but that the matter produced on the nipple of the cow is perfectly so."

In his description of cowpox Jenner stated that it appeared "on the nipples of the cow in the form of irregular pustules. At first it was palish-blue, rather livid, and surrounded by inflammation." Frequently, it degenerated into phagedenic ulcers. Soon the cow showed symptoms of indisposition and the milk lessened."

He then described how "inflamed spots appear on different parts of the hands of the domestic employed in milking, and sometimes on the wrists, which quickly run on to suppuration, first assuming the appearance of small vesications produced by a burn." Most commonly these local infections appeared " on the joints of the fingers and at their extremities, but whatever parts are affected, if the situation will permit, these superficial suppurations put on a circular form, with edges more elevated than their center, and of a color distinctly approaching blue." The condition lasted from one to three days "leaving ulcerated sores about the hands, which were very troublesome, often phagedenic, and heal slowly." He described how "other parts of the body might be inoculated, such as the lips, nostrils, and eyelids from being heedlessly rubbed or scratched with the patient's infected fingers."

He described the constitutional symptoms as "a mild septicemia with tumors in each axilla."

"What renders the cowpox virus so extremely singular is that the person, who has been thus infected, is ever after secure from the infection of small-pox, whether from exposure or inoculation."

"May I not congratulate my country and society at large on their beholding in the mild form of cowpox, an antidote that is capable of extirpating from the earth a disease, which is every hour devouring its victims; a disease that has ever been considered as the severest scourge of the human race?"

Precursors of Jenner.—It is now quite evident that Jenner was not the first to inoculate with cowpox with the object of giving protection against small-pox. The first known vaccinations were performed in 1774 by Benjamin Jesty, a farmer of Yeominster in Dorsetshire, who inoculated his wife and two sons, aged two and three years. "His vaccinations were successful and protected them, though they were exposed to small-pox. He himself had previously been accidentally inoculated with cowpox."

In 1791, Peter Plett of Holstein, a tutor, successfully vaccinated with a pocket knife three children of his employer. He made the incisions on the back of the hand between the thumb and finger, as he had seen physicians practice variolation. Three years later during an epidemic of small-pox, these children were the only ones who escaped.

Both Jesty and Plett were prompted in their action by the folklore statement of milk maids, namely, that those who suffered from cowpox were safe, if exposed to small-pox, but neither of them carried their investigations to the point of scientific demonstration and proof. This same statement of milk maids had come to the attention of Jobst Böse, a government official in Germany, but he paid little attention to it, further than repeat the assertion in 1769.

The credit, therefore, of giving vaccination to the world is due to Dr. Edward Jenner. He was born May 17, 1749, at Berkley in Gloucestershire, England. As a boy, he was always especially fond of natural history. At the age of 14 he decided to commence his education for the practice of medicine.

During his apprenticeship to Dr. Daniel Ludlow, a surgeon at Sudbury, near Bristol, he heard the remark of a milk maid, "I cannot get small-pox, because I have had cowpox." This remark expressed the belief prevalent at the time, that there sometimes existed on the udders of cows a sore or pustule, the matter of which, if placed on an abrasion on the hand of the milker, produced a peculiar sore, which was followed by a peculiar scar, and that this local ailment rendered its victim forever after immune from small-pox. Up to this time, this belief was considered by the medical profession merely as a superstitious vagary. It impressed Jenner, however, who took up the clew and followed it carefully for 20 years until he finally succeeded in solving the problem.

After seven years service with Daniel Ludlow he went to London, and entered the hospital service of John Hunter. Here he showed great ability and skill, especially in anatomy and natural history. In 1773 he began the practice of medicine and surgery in his own town, and in 1775 seriously began his studies in vaccination.

After five years devoted to the task of identifying the true cowpox vaccin, he was led to believe that this vaccin yielded its active virus in its purest state only at a certain stage of the development of the local lesion. After further experimentation, so great became his belief in the protective power of vaccin virus of cowpox, that he vaccinated his own son and then inoculated him with genuine small-pox. This hazardous experiment proved successful; the boy was immune.

In May, 1796, Sarah Nelmes, a dairy maid, became infected with cowpox through a scratch received from a thorn. Jenner transferred the virus from the eruption on her hand to the arm of James Phipps, a boy about eight years old.

A typical "take" followed. Later, in July, 1796, in order to learn if the boy was protected from the contagion of small-pox, "even though his constitutional symptoms had been slight, he inoculated him with variolus matter, immediately after it had been taken from a pustule of a case of small-pox. Several slight punctures and incisions were made in both arms, and the matter carefully inserted. No disease followed, and the arm appeared the same as was commonly seen, when a patient, who had previously suffered from cowpox or small-pox had variolus matter applied."

Several months later he again inoculated the boy, and again no sensible effect was produced on his constitution. Besides this one direct experiment Jenner inoculated with small-pox matter 10 other persons, who had previously had cowpox, all with the same negative results as with the boy.

He now had completed the circle of proof he had been looking for. He had produced with the vaccin lymph from cowpox a characteristic sore on the hand of the recipient. With lymph from the recipient, he had produced a second characteristic sore on the second recipient. And he proved that this second recipient could not be infected with small-pox, either by exposure or inoculation, and was also, as he then supposed, forever immune to the disease.

Jenner's first report appeared in 1798 in an unassuming pamphlet entitled "An inquiry into the causes and effects of variolæ vaccinæ." He presented the results of his observations to the Royal Society of London, but the paper was refused by the president "lest it should lessen the reputation he had already gained." For two or three months thereafter, Jenner tried to prove the results of vaccination in London, but could not find anyone who would submit himself for demonstration.

He then returned to Berkley, leaving with Mr. Cline, an eminent surgeon of St. Thomas Hospital, some of the vaccin lymph. Mr. Cline soon found an opportunity to insert some of the lymph, ostensibly as a counterirritant, into the hip of a boy "complaining of hip disease." A characteristic sore followed. After the boy had recovered from it, Mr. Cline inoculated him in three places with active small-pox matter. The boy remained utterly unharmed. After this demonstration Mr. Cline became an active advocate of Jenner's discovery, and succeeded in giving a great impetus to its adoption by the medical profession.

Thus in less than 12 months after publishing his pamphlet, Doctor Jenner's discovery was endorsed by a manifesto, signed by 73 of the most eminent medical men of London. Within two years it had been translated into nearly every language in Europe.

In 1799, tidings of the great discovery of vaccination reached the United States. Doctor Benjamin Waterhouse, Professor of the Practice of Medicine in Harvard University, succeeded in obtaining some of the virus and on July 8, 1800, vaccinated seven of his own children, six of whom went through the disease, vaccinia, in the usual manner. He later tested the efficiency of the protection by sending three of the children to the small-pox hospital. One of them, Daniel, aged eight, was, in addition, inoculated with small-pox by two punctures and by an infected thread drawn through the skin. No result beyond a slight local irritation was produced. The other two children did not suffer from the exposure.

This awakened an intense interest and excitement among the medical men of the United States, who thereupon proceeded to do a great deal of vaccinating. Unfortunately, they did not pay proper attention to the vaccin matter, to the technique of the operation, or to the progress of the pustule.

Furthermore, the practice was taken up by quacks, who vaccinated with all kinds of material. Naturally, harmful results followed, which threw the practice of vaccination into disrepute.

In 1801 Thomas Jefferson, then the President of the United States, received some of the vaccin virus from Doctor Waterhouse, who had just secured a second supply. With the assistance of his son-in-law he vaccinated about 200 people in Boston. This gave a fresh impulse to the practice and created a wider recognition of its value. President Jefferson also vaccinated an Indian chief and several of his companions, telling them that he was bestowing on them a gift from the Great Spirit which was going to protect them and free their nation from the dread disease, small-pox. The Indians later sent Jenner a belt of wampum and a letter of high praise to him and the Great Spirit.

President Thomas Jefferson, later, carried the practice to the southern states, where, through his influence, it was used to prevent the ravages of small-pox amongst the large black population.

Through the efforts of Doctor Benjamin Rush, Philadelphia was next to become a center for the dissemination of vaccination. In this way, the practice spread rapidly through the United States.

At the same time, the malpractices of Doctor Miller of New York and Doctor Woodville of London, gave to the spread of vaccination a decided setback. Either from carelessness, selfishness, or from the use of vaccin virus contaminated with true variolus matter, they succeeded in bringing considerable discredit upon the practice. It has been explained that Doctor Woodville first vaccinated a number of persons, and three to five days later inoculated them with small-pox, with the result that they suffered from both vaccinia and small-pox. Further, not appreciating the two affections, Doctor Woodville collected virus promiscuously from these doubly infected patients. Naturally the inoculation of this contaminated virus produced serious results. Nevertheless Doctor Waterhouse, a firm believer, continued vaccinating in spite of the ridicule and opposition of both the medical profession and the prejudiced public, so that he came to be called the "Jenner of America."

The efficiency of vaccination however, steadily progressed. Within six years after the publication of Jenner's pamphlet, the practice had been introduced and sanctioned in every civilized and semi-civilized country on the globe.

Various crowned heads of Europe set a good example by allowing themselves to be vaccinated and furthered progress by providing vaccination to their people free of cost. The Dowager Empress of Russia, Maria, presented Jenner with a diamond ring, and in honor of his discovery named the first child vaccinated in Russia, "Vaccinoff." Jenner was the recipient of all sorts of honors, public grants, and presents from numerous town, countries, and royal personages.

Protection by Vaccination.—In unprotected localities under former conditions, small-pox would be as prevalent and as fatal today as it ever was in the past. At the present time, however, epidemics occur not oftener than once in every 10 to 15 years, whereas formerly, they occurred every seven to eight years. And in every epidemic it had been shown, without exception, that the unvaccinated portion of the population has had a vastly greater proportionate attack rate and death-rate than the vaccinated.

Statistics bear overwhelming proof to the efficacy of vaccination. The following table shows the deaths per million population due to small-pox before and after the practice was established:

	Before vaccination	After vaccination
Sweden	2050	158
Prussia	5593	912
Austria	3905	841
Berlin	3422	176

In France, during the year 1802, there was only one case of small-pox among every 367 of the vaccinated population, whereas among the unvaccinated there was one case among every 12. Among the vaccinated, there occurred only one fatal case of small-pox among every 7166; among the unvaccinated, one fatal case among every 40. Of the 40,000 people in Marseilles in 1825, 30,000 had been vaccinated, 2000 had had small-pox; 8000 had neither been vaccinated nor had ever had the disease.

Of the 30,000 vaccinated, 2000 or one-fifteenth were seized; 20 died.

Of the 2000 protected by small-pox, 20 or one one-hundredth were seized; four died.

Of the 8000 unprotected, 4000 or one-half were seized; 1000 died.

Before compulsory vaccination was established in the German states, 66.5 per 1000 deaths were due to small-pox; after vaccination, 7.66 per 1000 deaths. In Bohemia the death rate per 100 was 5.1 in the vaccinated and 29.8 in the unvaccinated. In the Prussian army where vaccination was compulsory, there were, from 1873 to 1888, 300 cases of small-pox with three deaths. In the French army, where only a part of the men were vaccinated, there were, during this same period, 7807 cases with 698 deaths. In the Austrian army, where vaccination was even less thoroughly practiced than in the French army, there were 16,974 cases with 1034 deaths.

Of the 1300 population of Leicestershire, England, in 1882, all but two had been successfully vaccinated. In the epidemic of that year, all escaped the disease except these two, who died of it. In a severe epidemic of malignant or hemorrhagic small-pox in Berlin, the mortality rose to 81.25 per cent. in the unvaccinated, as compared with 14 per cent. in the vaccinated.

Through the courtesy of Surgeon-General M. W. Ireland, I have secured valuable information from the statistics of the United States Army during the World War, to prove the protection of vaccination against small-pox. I give similar statistics relating to the Spanish-American War and the Philippine Insurrection, and also, relating to the Union Army in the Civil War.

These statistics show a great advance in Preventive Medicine, and full credit must be given to the efficiency of our War Department.

I quote from his letter:

1. The number of officers and men enrolled in the United States Army during the World War was approximately 4,325,000.

2. The number vaccinated: Presumably all.

3. The number of soldiers admitted for small-pox was 853. In addition to this number 126 cases occurred among men admitted for other causes.

4. The number of deaths which occurred among soldiers admitted for small-pox was 14. In addition to this number, 1 death occurred among the 126 men who were admitted for other causes.

5. All cases of varioloid were included with small-pox.

6. The fatality rate of cases admitted for small-pox was 1.6 per cent. It was 1.5 per cent. including the cases and deaths occurring among soldiers admitted for other causes.

7. Remarks: (*a*) The annual admission rate for each 100,000 men was 21.

(*b*) The annual death rate per 100,000 men was 0.34.

(*c*) Of the primary admissions, 780 occurred among the troops in the United States and 24 among the troops in Europe.

(*d*) Among the primary admissions, 1 death occurred among the troops in the United States and 5 among those in Europe.

(*e*) During the Spanish-American War and Philippine Insurrection, there were 914 cases of small-pox with 265 deaths. This gives a fatality rate of 28.9 per cent., with an annual admission rate of 191 per 100,000 men and an annual death rate of 55 per 100,000 men.

(*f*) During the Civil War among the Union troops, there were 18,952 cases of small-pox with 7058 deaths. This gives a fatality rate of 37.2 per cent. with and annual admission rate of 800 per 100,000 men and an annual death rate of 275 per 100,000.

When small-pox was prevalent, the overwhelming majority of its victims were children, particularly those under 10 years of age, who contracted the disease with the frequency of measles today. In fact the susceptibility of infants was so universal that in Germany the disease was called "Kinderpocken." In Russia, there are statistics showing that at one time, one-seventh of all the children died of small-pox. In Great Britain, before the enactment of the compulsory vaccination laws, 70 to 80 per cent. of the annual small-pox mortality occurred among children under five years of age. As the vaccination laws became more stringent, the number of children attacked and the mortality rate were steadily reduced. In fact, the decline in the death-rate from small-pox has been limited mostly to children under 15 years of age. In England, the decrease in the death-rate of children has been greater than the total decrease in death-rate due to all other causes. In comparison, the death-rate from scarlet fever, measles and whooping-cough, has remained almost stationery during the past century.

There are numerous reports of vaccinated infants of a few months of age nursing at the breasts of mothers suffering from small-pox. In one case, in fact, the suckling infant kept open and painfully raw a pock mark on the areola of its mother's breast. Infants born during the progress of the disease and at once thoroughly vaccinated have remained with their mothers without ill effect.

There are also a few reported cases where a mother with small-pox was admitted to the hospital taking with her one infant vaccinated and one unvaccinated. In all these cases, the vaccinated infants remained well throughout the entire course of the mother's illness until her discharge, whereas the unvaccinated infants contracted the disease and rarely survived.

Vaccination in the last stages of pregnancy, though it may give immunity to the child, is not at all to be depended upon. Harper reports a case of a woman confined shortly after she had been vaccinated. Four days after birth, the baby became ill with small-pox and died.

In brief, the summary of the known figures shows that the death-rate among the vaccinated varies from an inappreciably small mortality up to 12.5 per cent., and among the unprotected, from 14.5 per cent. to 53.8 per cent. Statistics gathered in London in 1871 and 1872 show that while those who take small-pox a second time die in the proportion of 15.7 per 100, those who take the disease after vaccination, die only in the proportion of 3.3. per 100. This latter death-rate is as low, or even lower, than the mortality of the very mildest diseases.

In a Philadelphia epidemic of 5000 cases, the records of the Municipal Hospital show that 73 per cent. of the cases in unvaccinated infants under one year died, whereas there were no deaths among the vaccinated.

Duration of Protection. Revaccination.—Natural immunity to small-pox is exceptional, occurring probably in 1 per cent. or less of the population. In a few cases it has been shown that immunity after one vaccination endures for life, but in the large majority, the susceptibility to the disease returns. When Jenner first formulated his principle, he believed that one successful vaccination protected for life, but later, as his experience increased and he was enabled to make protracted investigations, he was forced to change his opinion in this regard. Doctor Goldsore, however, in 1804, was the first to announce that the protective effect of vaccination was diminished by the lapse of time. And in 1823, Doctor Herder at St. Petersburg further substantiated this discovery by pointing out that the prophylactic value of infantile vaccination became impaired about the age of 14.

It became apparent, then, that revaccination was as acute a necessity as the initial procedure. Recognizing this need, Germany, the first state to take such a step, passed a new law compelling all children to be vaccinated once in early infancy and again at puberty.

A German confederacy report states that 91 to 93 per cent. of revaccinations, performed 10 years after the primary vaccination, are successful. It contends that immunity begins to disappear after the second year, and that by the tenth year it is almost completely gone. Therefore, it says "a system of infantile vaccinaton, without revaccination later, is a halfway measure."

The British Royal Commission states that immunity generally lasts 9 to 10 years. The greater rapidity with which the effects of vaccinia upon the organism wear out in early life, as compared to mature age, is probably due to the fact that in early life, tissue change is more active and rapid, and that impressions on the organism are more easily effaced in the young than in the adult.

On the whole, however, it is probable that protection is lost in one-half of all people five years after the first vaccination, and in the other half by the tenth year. Therefore, revaccination for children every five to seven years, and oftener for those who have been exposed, is probably the safest plan. Very little is known as to whether vaccination immunity can be acquired through the breast milk of the mother.

In revaccination there are apparently three types of "take:" The first is as typical as the primary vaccination; the second follows a more rapid course, the period of incubation being shorter, so that the height of the pustular stage is reached on the sixth day; this type is called the "accelerated reaction." The third type may run an even more rapid, shorter, and milder course, so mild, in fact, that the vesicle does not develop. This type is called an "immediate reaction."

V. C. Vaughan, Jr., states that the vaccin causes a reaction in the body which leads to a ferment. This ferment subsequently causes a cleavage, not only of the vaccin body but also of the small-pox organism, and in that way affords protection. Thus, if we vaccinate a person, who already possesses the ferment, there is no reaction, while if the ferment is insufficient, there is either a mild accelerated reaction or an immediate one. The response to revaccination, which seems to vary in proportion to the amount of ferment remaining from the reaction induced by the primary inoculation, indicates to some extent, provided the virus is reliable, the degree of impaired or lessened immunity.

As small-pox may occur a second, a third and even a fourth time in some individuals, it is not strange that the vaccinated do not always escape. The disease, however, occurs much more frequently in those who have been vaccinated only once than in those who have been revaccinated, yet, even though repeated, vaccination is not as surely prophylactic as the disease itself.

In one report of 14,800 cases of small-pox occurring among people who had been vaccinated, it was shown that only four of them had ever been revaccinated. Another report has a record of 778 cases occurring in the vaccinated, only two of whom had been revaccinated previous to the recorded attack. In Berlin, of 1529 cases of small-pox in the vaccinated, only 19 occurred among those who had been revaccinated. In Leipsic, there were 1491 cases among those who had been vaccinated only once, and 13 among those who had been revaccinated; in Hamburg, 2208 cases in the vaccinated, and 59 in the revaccinated.

In some epidemics, where the contagion was of unusual virulence, the number of revaccinated people attacked by small-pox was considerably larger than in any of the above instances, but, compared with the number of cases among those who had been vaccinated only once, these statistics, like the above, represent the protective power of revaccination.

Various authors maintain that a number of vaccin inoculations made at the same time will prolong immunity and that a constant relation exists between the number of scars and the degree of immunity afforded. It has been stated likewise that the diameter of the scar is indicative of the degree of protection. Neither of these principles, however, has ever been satisfactorily proven. It is the character of the scar, rather than the size or the number, that is important.

Although it does not protect all people from small-pox, proper vaccination and revaccination will, nevertheless, reduce the mortality rate, even among the most susceptible; it will lessen the severity of the symptoms, especially of the secondary stage; lessen the complications; and shorten the convalescence, thus bringing about a modified form of the disease which is known as varioloid.

Vaccination immediately after exposure, if it "takes," gives absolute protection, because the period of incubation in vaccinia is shorter than that of small-pox. Vaccination, performed a few days after exposure, even though it "takes," gives, therefore, only partial protection. If performed seven days after exposure it gives little or no protection, and may run its course along with small-pox. If performed 10 days or more after exposure, it invariably fails to "take," and gives no protection whatsoever.

It has been assumed that when vaccination "takes," the recipient is susceptible to small-pox, and that when it does not "take" the recipient is naturally immune. Both of these assumptions, however, are questionable; the latter, in fact, having no justification whatever in actual practice.

Typical Course of Vaccinia Disease.—On the third or fourth day after vaccination, a faint redness appears about the point of inoculation, which gradually increases in size. At the exact point of inoculation there then appears a small, reddish, round, hard, flat, papule, its size depending upon the abrasion. On about the fifth day, the lesion begins to become vesicular, the vesiculation being first evident along the margin of the site of the inoculation. The vesicles gradually increase in size, and become filled with a thin, transparent lymph.

On about the eighth day the vesicle reaches its greatest perfection. It is then considerably elevated above the level of the surrounding skin, and contains lymph of a pearly or yellowish appearance. Close examination shows a depression in the center, similar to the umbilication of the variola vesicles. Jenner described the vesicle as having "an appearance not unlike a grain of wheat with a cleft or indentation in the center."

The inflammatory zone surrounding the point of vaccination, called the areola, closely parallels the growth of the vesicle, until the seventh or eighth day, when it rapidly increases in size and in redness and becomes tense and painful. Streaks of redness may now radiate a considerable distance away from the lesion.

This areola has been described as the reaction of the antibodies to the growth of the vaccin organisms. These vaccin organisms are digested, and their toxic products give rise to the constitutional symptoms. The change from the vesicle to the pustule marks the end of the vaccin colony. The appearance of a satisfactory areola, when not caused by mixed infection, is said to be a sign of the establishment of immunity.

With the formation of this acute areola, the adjacent lymphatic glands become enlarged and grow more or less painful. Then appear the constitutional symptoms, such as slight chilliness, malaise, loss of appetite, disturbed sleep, and a temperature of a degree or two. These symptoms, however, are not necessarily present in a typical case of vaccinia. This disease, like small-pox, varies in severity, both systemic and local, and in duration.

On the tenth to the twelfth day the pock begins to change; its contents become opaque or purulent, and desiccation appears in the center. There should be no deviation in the development of the pock. It should pass through the three stages of papulation, vesiculation with umbilication, and pustulation.

By about the fifteenth day, desiccation is usually completed. The crust is of a brown or mahogany color, rough on its exterior, thin at the edge and center, with a thick circular ridge between. It may not fall off until the end of the third or even the fourth week.

The scar is at first red, but in the course of a few months becomes paler than the surrounding skin. It is pitted or foveolated, and often shows radiating bands or striæ of cicatricial tissue.

Spurious or False "Takes."—There are a number of spurious forms of vaccination worthy of mention. The first is the raspberry excrescence which usually appears, from the third to the seventh day after vaccination, as a red elevation at the site of the inoculation. Instead, however, of advancing to the vesicular stage, it remains hard, dense, nodular and bright-red in color, looking not unlike a small nevus. It may remain in this condition for weeks or even months, and is never followed by a scar. It is supposed to result more often from the use of bovine than of human lymph. It is in no way protective against either variola or vaccinia.

False vaccinia sometimes shows itself, on the first or second day after vaccination, as a small pimple, developing a vesicle. This increases in size until the fourth or fifth day, when its progress becomes arrested. It then grows pale and dries up. At other times it progresses further in its development, but never shows the flattening or central depression so specifically characteristic of the true vaccination. The false pock is sometimes red and sometimes yellowish, but it never assumes the brilliant silvery luster which is the distinguishing mark of prophylactic vaccinia.

A false "take" may show, even as early as the second or third day, an unusual degree of inflammatory reaction, upon which, instead of a typical vesicle, there springs up with surprising rapidity a more or less conical or globular blister. This blister, which is thin-roofed, ruptures easily, and discharges a thin fluid, which is irritating to the surrounding area. It dries readily, without producing either a characteristic crust or scar. Though it may involve the adjacent lymphatic glands and produce some constitutional symptoms, it is not protective.

In successful vaccinations, we must always recognize the characteristic silvery appearance of the vesicle which, in the words of Jenner, resembles "a section of a pearl on a rose leaf."

The Vaccination Scar.—The danger of being infected with small-pox after a successful vaccination can be measured to a considerable extent by the character of the scar. A good scar is distinctly excavated, with a well-defined margin and a center that is smooth and somewhat striated. It has the appearance of having been stamped into the skin with a sharply cut die.

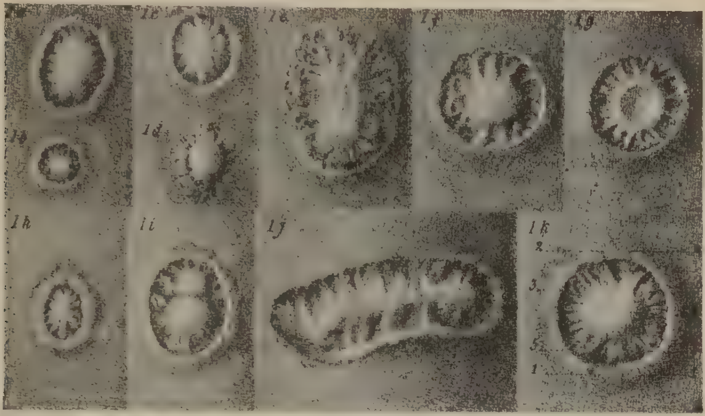

FIG. 22.—Various forms of good vaccinal scars, showing central elevated disk surrounded by a furrow with radiating bands; the scars look as if they had been punched out with a die. (After Denarp-Decanteleu.)

For several months after vaccination, the normal scar is red. Its color then gradually fades. The center, however, retains a pinkish

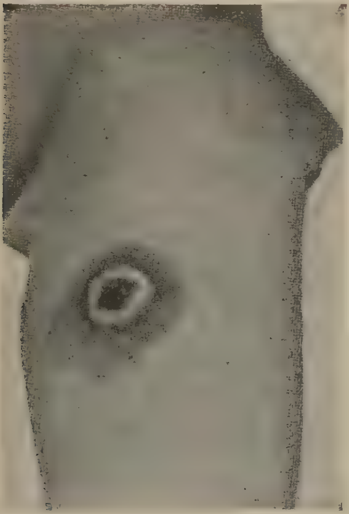

FIG. 23.—Vaccin vesicle upon the ninth day, showing more pronounced areola. (Welch and Schamberg.)

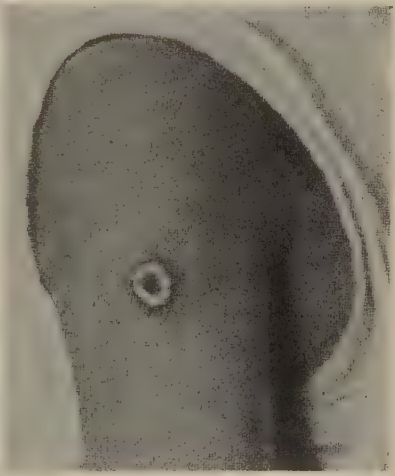

FIG. 24.—Vaccin vesicle upon the seventh day; areola just beginning. (Welch and Schamberg.)

tinge for a year or more. In its final appearance the scar is whiter than the surrounding skin and is encircled by a more or less deeply foveated ring, which corresponds to the active vesiculation. The center represents either the area of scarification or the cicatrix, following the separation of a more or less deep central slough.

The shape depends upon the size and character of the original scarification, and also upon the activity of the virus.

A fair scar is similar in appearance to a good scar except that its characteristics are much less pronounced.

A poor scar is irregular in outline with an ill-defined margin; it is not depressed, and has little or no foveation.

The excessive scar that may arise from a mixed infection can, as a rule, be easily recognized, because it has few of the characteristic appearances of the successful vaccination scar.

Number of Scars.—It was the custom formerly to make two inoculations and, in case of exposure, as many as four. Statistics seem to indicate that the extent of the protection is in direct proportion to the number of good scars. Out of 50,000 cases of small-pox, the following scar-percentage data were given:

Those with one scar..................	6.80 per cent. of the cases
Those with two scars.................	2.49 per cent. of the cases
Those with three scars................	1.42 per cent. of the cases
Those with four scars	0.67 per cent. of the cases

Among these 50,000 cases the character of the scar indicated the type of immunity as follows:

Those with scars of bad quality........	7.60 per cent. of the cases
Those with scars of tolerable quality....	2.35 per cent. of the cases
Those with scars of excellent quality....	1.22 per cent. of the cases

In Germany, whatever the form of scarification, it was declared by law that the scarified area should be at least ½ sq. in. in extent.

The mortality in reference to the number of scars is shown by the following table:

With one scar......................	2289 cases	Mortality was 5.4 per cent.
With two scars	2464 cases	Mortality was 3.6 per cent.
With three scars	1424 cases	Mortality was 3.1 per cent.
With four scars....................	1238 cases	Mortality was 1.6 per cent.

These all refer to primary vaccination and not to revaccination.

The number and quality of the scars seems conclusively to influence the mortality rate, the severity of the disease, and the depth of the pitting. But some authorities, like Welch, feel that one good scar affords fully as great a measure of protection as a number of scars.

Lymph. Human and Bovine.—In the earliest days of vaccination, the virus was collected from the udder of a cow suffering from cowpox, on about the fifth to the eighth day of the disease, just before the areola formed and before the lymph changed from the clear to the cloudy state. It was collected on silk threads, and was then either applied from these to the abraded skin or else drawn through as a seton. Other means of transportation consisted in placing the virus on lint held between glass plates, in bottles, or in the dry form, on lancets made of steel, silver, gold, or ivory. Jenner soon learned, however, in the practice of collecting, that vaccin virus easily deteriorated, particularly from the effects of fresh air and sunlight.

The supply of virus was greatly augmented by the discovery that the vesicle or scab of the person with a good "take" was fully as effective in producing vaccinia in the recipient as the lymph from the cow's udder. In early days, in fact, human vaccin virus was considered better than the animal variety. Every family physician, consequently, endeavored to have on hand a vaccin crust, which he believed to be pure. From this he took a fragment, which he moistened with water, and introduced into abrasions or scratches made upon the skin. But this transference of human lymph from person to person produced the risk of infection with such diseases as syphilis, and, as it was then supposed, scrofula, or tuberculosis, and so brought the use of this particular source of vaccin supply to an end.

It has been demonstrated that small-pox may be converted into cowpox, that by inoculating a calf with small-pox and passing the inoculation from calf to calf through several generations, the final inoculation will yield a pure vaccin virus. Thus the two, cowpox and small-pox, are modifications of the same disease, a fact which was not proven until after nearly a century of experiment. Duquemelle in 1800 was one of the earliest, if not the first, to use the calf as a source of supply. But it was not, however, until 1864 that this method of procuring lymph from the calf began to be extensively used.

Attenuation of vaccin virus, so that it will not excite severe symptoms and yet will at the same time afford full protection, has been brought about by passing the virus through eggs and animal juices, derived from the glands, such as the spleen, liver and the various others. Nevertheless, no method has as yet been devised which will provide a virus as good as that derived from the vesicle produced on cattle through inoculation.

In July, 1901, the United States government, through inter-state traffic regulation, assumed control of the production and sale of vaccin virus. Under government direction, milch calves are used for the production of the vaccin. These are first of all examined carefully by veterinary surgeons, particularly for any signs of tuberculosis, then they are quarantined for two weeks for the purpose of eliminating infectious conditions such as glanders, foot and mouth disease, tetanus, and the like, and also for the purpose of guarding against the development of fever, diarrheas, or skin eruptions.

Before being vaccinated, the calves are carefully washed, shaved, disinfected, and rendered as nearly aseptic, as regards themselves and their surroundings, as possible. They are then vaccinated, the groin and the belly being chosen as the sites for this operation, and are thereafter thoroughly protected from contamination. The animals are often fed on milk, not only because it is a clean food, but because it seems to make the skin more tender, thereby causing the vesicles to develop more abundantly and more typically.

When the papules are about to enter the vesicular stage, the calves are again surgically cleaned. The epidermis is removed by a spoon or curette, the whole papule being scraped off. The most active virus is obtained from deep curetting.

In 1891, Moncton Copeman announced that glycerine was a purifier of vaccin virus, acting as a differential germicide, by preserving the active principle of the virus, and destroying the frail, non-spore bearing bacilli. He also learned that no growth of yeasts or molds could occur in 60 per cent. glycerine, the antiseptic action being one of dehydration. For the purpose, therefore, of purifying the vaccin, the curetted pulp is mixed with a two to four parts of a 50 per cent. glycerine solution, and the two are thoroughly ground together until the suspension is uniform. If a higher than 50 per cent. glycerine solution is used, the efficiency of the vaccin is impaired.

This mixture of 50 per cent. glycerine and pulp, the so-called "green vaccin," is then put in tubes and placed in cold storage to ripen, a process which lasts from 30 to 60 days to sometimes 6 and even 12 months. During this time, the vaccin virus must be kept free from exposure to light and air to preserve its potency and insure the ripening process. It must also be examined every 10 to 15 days until the bacteria are found to be virtually absent. The "unripe" or "green" glycerinized lymph should never be used, as it may produce various kinds of sores, some of them serious, with severe constitutional symptoms.

Meantime to determine that the calf is free from all disease, it is killed and carefully examined. Then to find out if the vaccin is free from all specific germs, such as tetanus, erysipelas, etc., the material is injected into guinea pigs. Finally, it is tested on children in reference to its potency, and if found satisfactory, is placed on the market.

It is necessary to exercise care in the storage of vaccin lymph, particularly in the matter of temperature, for both heat and cold have deleterious effects upon it. The rapidity of the elimination of bacteria depends upon the temperature above 10°C. in which the virus is stored. Nevertheless, continued exposure to 10°C., which is ice-chest temperature, will destroy the potency of the virus in three to six months. Exposure to 23 to 30°C., or room temperature, will destroy it in one to three weeks; 37C., or blood temperature, in three to four days; while exposure to 60°C. will destroy the potency in five minutes. On the other hand, if the vaccin lymph is kept at or below the freezing point, the glycerine will not only fail to kill the extraneous bacteria, but may even contribute to their activity and number. The pathogenesis, however, of the contained staphylococcus and streptococcus is usually lost long before the potency of the virus itself. Lastly, it must be remembered that if the vaccin lymph is kept too long, even under proper conditions, the glycerine destroys not only the bacteria, but later the efficiency of the virus itself.

It has been fully shown that the dry points, as compared with the glycerinized lymph, not only contain twice the number of bacteria, but preserve the potency of the virus for a relatively shorter time. In consequence, their preparation and sale in the United States was discontinued by law Jan. 1, 1910. On the other hand, glycerine is said to be preservative of such infections at tetanus and malignant edema. Hence, animal inoculation with the glycerinized lymph is essential to prove its safety.

The rapidity of the elimination of bacteria depends upon the temperature above 10°C. in which the virus is stored.

Sterile Vaccin Virus.—Numerous methods have been tried for producing a sterile virus. Fournet accomplished this end by the use of ether, the virus remaining potent for weeks. Noguchi sterilized the virus by first using ether, and then injecting it into the testicles of rabbits or bulls, where it increases in amount, reaching its maximum in four or five days, remaining stationary until the eighth day, and then diminishing gradually, until, at the end of five weeks, it has disappeared.

Noguchi found the rabbit more successful than the bull for producing a potent virus in this manner. Before the virus can be made adaptable to the testicle, however, it is necessary to pass it through several rabbits. Its strength in the first transfer may be less than that of the original specimen, but subsequently, the activity rises until it reaches its maximum, as strong as the original skin strain. The testes of the rabbit, after being finally injected with the virus, are removed at the proper time, ground with a sterile salt solution, and stored as a stock emulsion. Noguchi claims that the virus produced in this way becomes progressively stronger and that a dilution of 1:100,000 may produce a typical vesicle. The course of vaccination is the same as with the bovine virus, except that all symptoms of complicating infection are absent.

A sterile virus has been produced by Gaylord and Wheeler with potassium cyanide which destroys the bacteria without lessening the efficiency of the pulp. A. B. Green proved that chloroform, 1:200 of distilled water, destroys the bacteria without interfering with its potency. The Japanese use 1 per cent. carbolic acid in glycerine. The lymph is thus freed in 4 to 10 days of all non- spore forming bacteria. Tuluol in the proportion of two parts to 10 of pulp renders the lymph practically free of bacteria in four days, and, as far as is now known, does not materially reduce the activity of the virus. Other drugs have been advised to purify the virus. It is said that in Germany bacterial control is now almost entirely abandoned.

Technic of Vaccination.—The dread of vaccination by the laity would be greatly decreased, if each vaccinator looked upon it as a minor surgical operation, and followed the principles of aseptic surgery, both in the operation and aftercare. It must be remembered that sepsis is the result, not of the vaccination, but of improper technic or subsequent mismanagement.

In performing the operation of vaccination it is wise: (1) To wash the arm with green soap and water.

2. Scrub the part with alcohol, using sterile gauze.
3. Scrub with ether, using sterile gauze.
4. Flame or boil the scarifier. Short linear scarifications are better.
5. Rub in the virus with sterile points.
6. Allow area to dry and cover with sterile dressings held by straps.
7. Instruct caretaker as to aftertreatment.
8. See that the instructions are carried out, and
9. Treat as an infected wound on evidence of any complicating infection.

Immunity appears about the eighth day of the vaccination. If it "takes," whether primary or revaccination, as previously stated, the subject probably was susceptible to small-pox. But if it fails to "take," it does not necessarily follow that he was immune. A sore arm does not confer immunity, unless it is the specific sore of cowpox.

Care of Vaccinated Wound.—Almost all of the accidents of vaccination are avoidable. Keep the wound free from complicating infections through careful protection. Scratching with dirty nails often causes serious trouble.

The vaccination should be observed by the physician, as often as is necessary, to make certain that it is a good "take," and to advise as to the dressings. These should be aseptic. The shield has been almost universally condemned, since it keeps the vaccination focus too warm and too moist, and may thus become an incubator for bacteria of all kinds. If kept properly sterile, however, it may at times be cautiously used; for instance, early after the operation to allow the virus to dry, and later to prevent sticking of the dressings. Without doubt, sterile dressings are best. The vaccination area should be frequently washed with boric acid solution, and the dressings changed as frequently as is necessary to keep the part clean and the dressings from sticking.

It is wise to keep the central scab as dry as possible, in order that it may not be too early pulled off by adhering dressings. This dryness can be maintained to a large extent by the use of boric acid dusting powder.

Various methods have been tried of minimizing the discomfort of vaccinia. The consensus of opinion maintains, however, that asepsis treatment of the vesicle is about the only method that will influence to any marked degree the duration and severity of vaccinia. Schamberg painted the area with 4 per cent. alcoholic picric acid solution 48 hours after vaccination. Kolmer painted it with iodin; others have used pastes, but, on the whole, no special advantage has been noted as the result of these treatments. Application of 50 per cent. alcohol has been advised to relieve the soreness of the areola.

The choice of site for making the vaccination is at the insertion of the deltoid on the arm or just below the head of the fibula on the leg, in neither of which places is there much muscle action. The arm is preferred to the leg, because there is much less danger, either of trauma or of secondary infection from street dirt.

Small inoculations, either single or multiple, give rise to small vesicles, which are not easily broken, and which do not foster anaërobic conditions, and a central slough.

In scarifying the selected site, simply remove the epidermis, without going deep enough to cause bleeding. This operation may be performed with any instrument. Force recommends the scarifier used for the von Pirquet test for tuberculosis, because:

1. If the scarifier is steel and has a sharp edge, the epidermis is removed without bruising the tissue.
2. The results are more uniform.
3. Percentage of failures is reported less.
4. It is safer, because there is no scab favoring the growth of anaërobic bacteria.
5. Economy of virus; by this method 1 c.c. of lymph has vaccinated 285 people.
6. Absence of psychic shock.
7. There is a single vesicle instead of a number running together.

The drawback to this method is the smallness of the area scarified, the size of which is infinitesimal compared to the ½ in. scar demanded in Germany.

Sternberg says that "immunity may be induced by a subcutaneous inoculation of vaccin virus without the apperance of a vaccin vesicle." And it is probable that the subcutaneous injection of lymph preserved in glycerine would give protection without any of the septic complications so common as a result of vaccination by the usual methods."

Bacteriology.—No specific germ has as yet been found, either in small-pox or vaccinia. Various bacteria are found in both human and bovine virus, but they are the ones ordinarily contained in the skin, such as the staphylococcus aureus, the streptococcus, and others. It is probable, however, that the pyogenic cocci are of great importance as complicating factors in vaccinia.

Extended experiments indicate that the germ of vaccinia does not belong to the class of microörganisms known as bacteria. The specific principle exists chiefly in the epidermal lesions, the pulp containing more potent and more concentrated virus than the lymph. By filtration, sedimentation and diffusion, the liquid or soluble part of vaccin has been separated from the insoluble. It has then been found that the smallest part of the insoluble substances produces vaccinia, whereas the fluid or soluble part remains impotent in this respect.

Some authorities claim that vaccin virus is filtrable; others flatly contradict this statement. Park and Williams maintained that glycerinated virus, filtered through two or three thicknesses of finest filter paper, gives a slightly opalescent filtrate, which, in the hanging drop and under high magnification, shows many tiny granules with an occasional larger one. This filtrate, though it produces no growth on culture media, gives an abundant typical reaction. Park was unable to filter vaccin virus through a Berkefeld filter under 40 lb. pressure, but later thought his failure might be due to lack of dilution. Bertarelli and a few others state that vaccin virus is slightly filtrable under pressure; while Wolbach, without hesitation, classifies it as a filtrable virus.

From a hanging drop of virus, W. E. DeKorte of London, England, found, without other manipulation, large numbers of unicellular elements, which on a warm stage, showed amoeboid movements. In 1886 and 1887, Van der Loeff and L. Pfeiffer found what they thought to be protozoa, which were called "vaccin bodies." In 1892 Guarnieri studied these structures and believed he saw amoeboid movements in some of them. He named this species of protozoa Cytoryctes Vacciniæ. These bodies are spheroidal or oval structures, and readily stain with various dyes. The central portion gives in general the staining characters of nuclear substances. A peripheral zone is sometimes differentiated by cytoplasmic stains.

These bodies lie close upon the border of the nucleus of the epithelial cells, and sometimes in a depression in the nuclear border. There are larger and smaller forms, the larger being associated with older lesions, and apparently undergoing segmentation. Their substance resembles protoplasm, and possesses the staining reaction of chromatin. Monti, Clark, and others confirmed Guarnieri's statements. But Ewing, while admitting that vaccin bodies are probably specific for variola, calls attention to the fact that specific cell degenerations or inclusions are found in various infectious processes, such as diphtheria, measles, glanders, etc., and that they cannot in any way be regarded as related to the etiology of these diseases. He suggests the probability of similar interpretation of vaccin bodies.

In 1903, Councilman, Brinckerhoff, and Tyzzer confirmed for the most part the observations of Guarnieri. They not only found the vaccin bodies in the lower layers of the skin epithelia of the lesion, but also discovered morphological evidence of their segmentation, and of the formation of spore-like structures. Councilman found within the nucleus of the epithelial cells, circular ring-like structures with a central dot, occurring singly or in clusters. These intra-nuclear structures he believed to be developed from the spore-like bodies which result from the segmentation of the intra-cellular vaccin bodies. He believed that the vaccin bodies, or small-pox parasite, pass through two cycles in their development, one intra-cellular and one intra-nuclear, and that in vaccinia, there is only one cycle, the intra-cellular. He further explained that the Cytoryctes, Vacciniæ, in their life cycle, asexually divide and multiply in the cytoplasm of the epithelial cell; that when they once lost their power to generate by sexual division they never regained it; and that small-pox is caused by the combined sexual and asexual cycle of the same parasite. Thus we have the explanation of the modification of small-pox to vaccinia.

The duality of small-pox and vaccinia has been much discussed. By passing small-pox through the calf, it can be modified so that on re-inoculation it produces vaccinia; but vaccinia, though it protects against small-pox, can never be modified to produce that disease. These two elements, the intra-cellular and the intra-nuclear bodies, may explain the duality of these diseases.

Loeb and Gorham suggested that because the active principle of vaccin virus resisted the germicidal effect of potassium cyanide, it must be a protozoon.

Some consider the specific cause a submicroscopic microörganism inclosed in a cell which gets its nourishment from the nuclear proteids, and which, being inclosed in this cell reticulum, cannot therefore pass through a filter. Klein found a bacillus, a spore bearer, which appeared on the fifth day of the vesicle and later disappeared. This bacillus, after being grown, was vaccinated into infants and produced vaccinia.

The opinion is about equally divided between the two hypotheses, protozoa on the one hand and microörganisms of unknown nature on the other; and it will require further study before the specific cause in small-pox, as in hydrophobia, is definitely settled.

Complications of Vaccination.—**Tetanus** stands out as one of the most important complications. While its occurrence is rare, its coincident development is always most impressive. It occurred 13 times in 500,000 vaccinations among private firms. From 1904 to 1913, only 41 authenticated cases were found in over 31,000,000 vaccinations. Of 585,000 vaccinations performed in the United States Army and Navy during 11 years up to 1913, only six cases of tetanus developed.

It is a well-established fact in tetanus developing in cases not associated with vaccination, that the shorter the period of incubation the more fatal the disease. For instance, of the 588 cases collected by Anders and Morgan, where the period of incubation was 10 days or less, the mortality was 61.7 per cent., and where it was over 10 days, the mortality was 41.5 per cent.

Elgin reported 82 cases of tetanus following vaccination, occurring in the United States and Canada from 1899 to 1914, of which all but four died, thus making a mortality rate of about 95 per cent. One-half of these deaths occurred within 48 hours. In 69 per cent. of Elgin's cases, tetanus developed over two weeks after vaccination. In another report of 93 cases of tetanus developing after vaccination, the mortality rate was 75.2 per cent. and the average appearance of the disease was 20.7 days. The high mortality rates of 69 per cent. and 75.2 per cent. in these two sets of reported cases, indicate the intensity of the infection and, just as certainly, the shortness of the period of incubation. Hence, this evidence quite conclusively points to the fact that the tetanus infection was post-vaccinal, probably occurring after the tenth day.

J. F. Anderson vaccinated monkeys of the rhesus type and guinea pigs, both susceptible to tetanus, with vaccin virus heavily contaminated with tetanus spores. None showed any evidence of tetanus, even though germs of the disease were easily found in the scabs or crusts. It was explained that the high acidity due to the presence of the staphylococcus, the bacillus coli, and the bacillus Welchii occurred either while the tetanus spore was germinating or before this process, and hence caused it to lie dormant. This experiment, however, does not in the least minimize the necessity of eliminating tetanus germs from vaccin virus.

As tetanus is commonest in the late summer and fall, it has been frequently advised to vaccinate in the winter and spring, unless small-pox is prevalent.

Tuberculosis.—The inoculation of tuberculosis by a superficial scratch is very rare. A tubercular node on the site of a vaccination scar has never been seen. Were a scratch sufficient, tuberculosis following autopsies would be commonly recorded. A rather deep incision is necessary for local infection. On the whole, however, the danger of lighting up a latent tuberculosis by vaccination is nothing as compared to the danger from small-pox.

Copeman says, "the tubercle bacillus is effectively destroyed even when large quantities of virulent cultures have been purposely added to the glycerinated lymph." This statement impresses the writer as rather extravagant, and he is sure he would not be willing to subject himself or his patients to the dangers of a lymph contaminated by tubercle bacilli.

There are numerous other complications which may arise through infections, such as erysipelas, leprosy and impetigo. Impetigo is fairly common. Erysipelas may occur any time, but is oftenest seen during the second week. It occurs much less frequently since bovine virus has been used. All these complicating infectious conditions, however, have been tremendously decreased, since the vaccinated wounds have been treated with surgical asepsis.

Inflammatory conditions, such as eczema and psoriasis, or erythema multiforme, and urticaria, may occur with vaccination or be lighted up by it, but they are not in any way due to the specific infection from the disease. Abscesses, furuncles, lymphangitis, cellulitis, phlebitis, even pyemia, may occur, but they are rare and generally not serious.

Effect of Vaccination on the Blood.—In the red cells and hemoglobin, there is no change. There is apt to be a leukocytosis of about 15,000, consisting mostly of polynuclear neutrophiles, which, considering the local focus, is a relatively high increase.

The blood serum of immune animals contains a substance in solution, which frequently destroys the specific virulence of vaccin virus when brought in contact with it. This substance is not present in sufficient amount to make the blood serum of immune animals available for the production of immunity in man, or for the treatment of variola. But it may perhaps be obtained in a concentrated form by some chemical method, and, in that case, prove useful, and possibly specific, as a therapeutic agent in this disease.

Passive immunization of susceptible animals against cowpox and small-pox, from transfusion of a large amount of blood serum taken from an immune animal, has been occasionally successful and frequently unsuccessful.

The antibodies of cowpox and small-pox are undoubtedly identical. Cowpox is carried only by direct inoculation of the denuded skin, whereas small-pox is carried by the air.

Measles and small-pox resemble each other in that the spread of each is not dependent upon any sanitary defect.

The Royal Commission on Vaccination says: "We see nothing to warrant the conclusion that in this country vaccination might be safely abandoned and replaced by isolation." Vaccination without coöperation of sanitary measures is much more efficient than the reverse.

Laws Concerning Vaccination.—England.—The first vaccination act, which was passed in 1840, made the operation of vaccination entirely voluntary. In this law inoculation with small-pox, or variolation, was forbidden and made a penal offense. In 1853 a compulsory vaccination law was enacted which required that all infants should be vaccinated with human lymph before three months of age. In 1867, an act was passed enjoining and encouraging revaccination. In 1898, bovine vaccin virus was designated to take the place of human virus; domiciliary vaccination was designated in place of vaccination stations; the period of infantile vaccination was changed to the age of three to six months; and the so-called "conscientious objector" clause was included.

France.—In 1902, a law was enacted compelling vaccination during first year of life and revaccination both at 11 and 21 years of age. Three inoculations were deemed necessary for successful vaccination; the use of bovine virus was advised. All conscripts to the army were revaccinated.

Germany.—In 1874, a law was passed compelling vaccination during first or second year of life and revaccination at 13 years of age. This law required that the abraded area for vaccination should equal one-half of a square inch. Two inoculations were necessary, and inspection was required between the sixth and ninth day after the operation. Small-pox has thereby been virtually eradicated, and epidemics are unknown.

Austria.—The earliest legal regulations, which were introduced in 1808, amounted to but little. In 1900 indirect compulsion was enforced. Now all must be vaccinated before they enter schools, offices, public institutions or military service. As regards schools, however, the law can easily be evaded.

Russia.—Vaccination has never been made compulsory by a national act, but has, however, been in force indirectly, since without successful vaccination, one is forbidden entrance to schools, universities, civil or military service. Russia is a badly vaccinated country generally, and small-pox epidemics are not uncommon.

Italy.—Compulsory vaccination within six months of birth was required by law in 1888. If the primary vaccination fails, revaccination is obligatory within one year. These laws are strictly enforced.

Switzerland.—In 16 cantons, vaccination is compulsory, while in the remaining nine, it is discretionary. In these nine cantons, however, it is enforced indirectly, being necessary before entrance to school or official life. Revaccinations between 12 and 13 years is obligatory.

Norway.—Vaccination is not compulsory by law, but is compelled indirectly through school, university, army and navy regulations.

Sweden.—Compulsory vaccination by the end of the second year, with six to eight vesicles, is enforced.

United States.—The operation of vaccination is regulated by the different states. The general tendency has been toward less stringent laws. In those states in which vaccination is not obligatory, it is indirectly enforced through school regulations. The only control the United States government has over vaccination is through the regulation of inter-state traffic. Vaccination before entering military service is compulsory.

CHAPTER CXLVI

VARICELLA

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Varicella is an acute and very infectious disease, which occurs generally in children. Its chief characteristic is an eruption of vesicles, which develop in crops, and dry up in a few days, leaving a granular scab. It is ordinarily the mildest and least important of the infectious diseases, and has little or no mortality, unless associated with severe complications.

Synonyms.—Chicken-pox, Wind blättern, Wasserpocken, Schafpocken, Variola, Notlia, Sen Spuria, and Ravaglione.

History.—Very little mention was made of varicella by the earliest writers. In 1550, Ingrassias, Vidus Vidius and also Duncan Liddle gave the first definite description of the disease. In 1641, Riviere described the disease in France, and in 1690, Morton gave it the name chicken-pox from the word cicer, a chicken pea. Vogel, in 1764, gave to the disease the latin name Varicella, which is the diminutive of varus, a pimple.

Fuller, in 1730, was one of the earliest to affirm the lack of identity between variola and varicella. Heberden, in 1867, gave the world the first accurate and comprehensive description of the disease. Both of these men established some points of differentiation from variola vera, the most important being that variola and varicella were not protective against each other.

Varicella has always been more or less confused with small-pox or varioloid, and while now recognized as a separate and definite disease, it is still the name often given to the very mild forms of small-pox. The fact that these two diseases gave no protection to each other was the stimulus to the early clinicians and writers to try to differentiate between them, and the controversy as to the identity and lack of identity of the two was carried on for years with considerable spirit. The discovery of vaccination by Jenner, in 1798, which increased the number of cases of varioloid, likewise increased the intensity of the controversy. In 1805, Franck and Heim of Germany contributed important data, the latter calling attention to the lack of inoculability of varicella. Thompson of Edinburgh studied carefully an epidemic which prevailed in Scotland in 1818 and 1819, and came to the conclusion that varicella was a mild manifestation of variola. Hebra, Kaposi, Bruyelle and Kassowitz also shared the view of the common origin of varicella and variola. Hebra formulated the following nomenclature: All cases requiring 14 days or less for their course he called varicella; all cases terminating in about three weeks he termed varioloid; and all cases running a course of four weeks or more, variola vera. Hessa in 1829 published a complete monograph on the subject. Trousseau was one of the first to separate the two diseases, but varicella was not fully accepted as a separate disease until the epidemic of small-pox in Germany in 1870–1873, when the two diseases were carefully studied from all viewpoints and their lack of unity established. It was then proven that (*a*) inoculation with varicella produces only varicella; (*b*) varicella cannot produce variola, and *vice versa;* and (*c*) varicella does not protect against variola, and *vice versa.*

Varicella exists throughout the whole year, though it is possibly more prevalent in the fall, on account of the attendance at school. In large cities, it usually exists sporadically with epidemics occurring at frequent and irregular intervals. At present, varicella is looked upon as a disease of childhood, and small-pox, a disease of the adult, and this accepted rule applies so generally that varicella in an adult is always looked upon with grave suspicion. Many clinicians of broad experience in infectious diseases have never seen a case of varicella in the adult. In fact Hutchinson of London has claimed that there is an "almost absolute immunity of adults." Graham states that it is seldom seen after 10 years of age, and Eustace Smith, that the age by preference is two to six years. Gregory reports seven cases in adults; MacCombie seven cases; and men like J. Lewis Smith and Professor Flint report only one case each. On the other hand, Welch and Schamberg report having seen many cases in the adult, and claim that it is not so rare at this stage of life as is generally stated.

The youngest case of varicella which I have found reported was one described by F. C. Pridham, in which the infant was four hours old, and had a typical rash on the trunk, scalp, and face. It was born in a house where the disease had been present 14 days before.

As a rule, infants under six months of age seem to have a certain immunity, but this is not so marked as the immunity against scarlet fever or measles.

Etiology.—The infectious property of this disease is short-lived. It does not easily cling to clothing. It does not remain active in dwellings as long as scarlet fever. Direct exposure is generally necessary, but it may travel through the air for a short distance; may spread through infected articles; and possibly be carried by a third person. The contagion probably gains entrance through the respiratory passages through contact. It is possible for the disease to be transferred before the appearance of the eruption, just as it is possible for small-pox to be transmitted during its initial stage.

The duration of the transmission of the infection is not definitely known; neither is it known if the infection exists in the crusts, as it does in small-pox. It is consequently wise to isolate the patient until the skin is free from the original crusts, but crusts, due to secondary infection, are not infectious.

The specific principle of varicella, like that of small-pox, is not yet known. Bryce of Edinburgh, in 1816, inoculated with the vesicular fluid in all stages of the disease, but was never successful. Hessa in 1829 compiled data of 113 inoculations. In 87, there was no result; in 17, merely local manifestations; and in nine, there occurred a general eruption. Material for inoculation was taken from the clear fluid, the opaque or purulent fluid, and from the crusts. Vetter, in 1864, stated that varicella could not be carried by inoculation of the vesicular contents, a statement which Heberden and Fleischman later confirmed. But Steiner, in 1875, inoculated 10 children, in eight of whom, the results were successful. Two of the successfully inoculated had been previously vaccinated. He demonstrated that the period of incubation from inoculation was eight days, i.e., until the appearance of the vesicles and the general symptoms. In his cases, there was no local response.

In 1903, David Smallpiece inoculated a girl of 11 years with fluid taken from the vesicle on the second day. In eight days, the site showed irritation and "on the ninth day a papule, which gave the appearance as if a small vesicle had been rubbed off." While there were no constitutional symptoms at that time, later nausea and some fever developed. At this time, a general accuminated papillary eruption appeared.

In chicken-pox, inoculation is difficult, while in small-pox, it is easy. The inoculation of one never has succeeded in causing the other. Vaccination against small-pox is successful, but it does not protect against chicken-pox.

Clinical experience and experimental data indicate quite conclusively, according to J. A. Kolmer, that the virus, as in small-pox, is present in the skin lesions; that it is probably inspired, and that, in passing through the body fluids, it reaches the skin, for which it has a selective affinity.

While varicella is extremely contagious, its infecting power is not as intense as that of measles or small-pox, and it is easier to control by isolation than the latter diseases.

Page saw simultaneously in one case variola, varicella and vaccinia.

Period of Incubation.—The older authorities declared that the period of incubation lasted from four to six days. Steiner, by inoculation, demonstrated it to be eight days. More recently, with the infection traveling in the ordinary way, it has been considered to vary from 11 to 25 days, but it is oftenest 14 to 16 days.

Bacteriology.—Nuclear and cytoplasmic inclusions are found, according to Tyzzer, in all varicellar lesions, but they are without definite form or structure, and without evidence of multiplication. No conclusion has been reached that they are parasitic organisms. He gives a differential diagnosis of the contents of the vesicles in varicella and small-pox. The former contain large multi-nucleated cells, which are not present in the latter disease. Tyzzer looks upon this point as quite a reliable test.

The effect on the rabbit's cornea differs widely. In small-pox inoculation, the cornea roughens in 24 to 48 hours, and passes through definite stages. This does not occur with inoculation of the contents of varicella vesicles.

De Korte says the parasite of varicella can be found the first, second and third days of the eruption. He considers it a protozoan, resembling the parasite found in variola and vaccination; he declares that it is motile, and can be seen in the hanging drop. Pfeiffer also describes a protozoan.

Bareggi describes ovoid microörganisms in the leukocytes on the fifth day, which, when used for inoculation, have produced varicella in children. Rille says that, as the vesicular contents become opaque or purulent, these microörganisms grow less numerous.

A. Ischamer mentions finding a hitherto unknown micrococcus, distinct from the one he obtained from variola. He did not, however, confirm his opinion by inoculating children, but claimed that it aided in proving the non-identity of varicella with variola.

Immunology.—Few possess a natural immunity. Race does not seem to afford any protection, for the white and the black contract the disease with equal susceptibility. One attack of varicella usually confers an active immunity for the balance of life. Thus, it is possible that antibodies to the virus persist in the body fluid for a long time. Kolmer says that immunity principles have not yet been detected by complement fixation.

Second attacks are rare. Gerhart and Heim each report seeing three attacks in one child. Vetter reports two attacks within 14 days in the child of a physician. Neale reports a second attack after a 10 day interval. Trousseau, Kassowitz, Hufeland and Constatt report second attacks, but these, on the whole, may be considered more rare than second attacks of small-pox.

Pathology.—The earliest changes are found in the maculo-papular lesion, which precedes the vesicle. Microscopical examination of the lesion, in the different stages, shows that the processes are of the same nature, differing only in intensity and in duration. According to Tyzzer and Councilman, there is first a swelling of the cytoplasm and of the nuclei of the cells, and second, a liquefaction or ballooning degeneration of the cells, under which fluid develops. The nuclei divide by direct division until a large number are grouped in the center of the cell. The lesion may develop from several centers. The fluid is confined in compartments, separated by septa. These partitions radiate downward from the covering rather than upward from the central floor, as is described in small-pox. The septa moreover are not as strong as those in the vesicles of small-pox. If the fluid of the liquefied cells is thrown out only in small amount, the septa may persist, but if in large amount, they either disappear from rupture, or are absorbed by pressure. This explains why some of the vesicles are unilocular and some multilocular, and also, since most of them in their full development are unilocular, why they are not umbilicated.

The base of the vesicle is concave, and extends down to the level of the papillæ, which are somewhat swollen and enlarged and project slightly into the cavity.

In the corium, the vessels are dilated, and there is a proliferation of the endolethial cells and of the connective tissue cells. A few polynuclear cells are also found in the corium.

The fluid of the vesicles, unless infected by bacteria, is serous, and is either alkaline in nature or weakly neutral. It is at first clear, contains fibrin and coagulates spontaneously when removed. The cells found in the fluid in the early stages of varicella are, for the most part, polynuclear, whereas in variola, they are apt to be mononuclear. In addition, the fluid contains a few degenerate or necrotic epithelial cells. Later, a large number of phagocytic endolethial cells are found.

The active destructive process is immediately followed by repair. The epidermis grows in, closing the defect, and the corium returns to its normal condition.

Cicatrices are not unusual, particularly on the forehead. They are little or slightly depressed; are a little paler than the surrounding skin; are smooth; and they vary in size up to 4 mm. Caused by the superficial destruction of the corium, they affect the papillæ only slightly, and are never deep enough to involve the true skin, the sweat glands, or the hair follicles. Hence they are never foveated. The more the mixed infection, the greater is the scar.

The involvement of any of the internal organs has not been definitely determined.

Symptoms.—Prodromal symptoms may or may not appear. Henoch stated that all such symptoms were accidental. When they appear, they are usually mild and vary in duration from a few hours to two or three days.

The constitutional symptoms are generally mild in nature; often they are completely absent. Nevertheless the toxicity of varicella may produce severe symptoms, so that the disease, on very rare occasions, is ushered in by delirium, convulsions or coma.

The commonest symptoms are malaise and a slight temperature, which rises either before the appearance of the rash, or is concurrent with it. Possibly the temperature rises with each crop of the rash, falling to normal between times. The height ranges from 100°F. to 102°F., though a temperature of 106°F. has been recorded. Should the vesicles become infected, the temperature is higher, and the daily variation greater. In the ordinary case, however, the temperature is apt to be highest on the second day, without following a characteristic course. It lasts a day or so; if found to persist longer, it is usually indicative of some complication.

Besides malaise and fever, we may have anorexia, more or less restlessness, disturbed sleep, sometimes pain in the abdomen, with occasionally vomiting. Sometimes, though rarely, the back and joint pains may be severe enough to suggest variola. With the onset of the rash, there is apt to be a burning or stinging sensation. Should the genital organs or other mucous membranes be involved by the rash, symptoms referring to the part affected, may arise. Dizziness is mentioned as fairly common; and, if the intoxication is severe, even delirium may be present.

Rash.—Prodromal rashes of an erythematous type occur occasionally.

The rash may be the first symptoms noted. It appears on the first to the third day of the disease; occurs in crops, two or three in number, sometimes more; manifests itself on successive days; and lasts for a week or more before it reaches the stage where the crusts fall off.

The favorite site is the back, chest, abdomen and scalp. The rash occurs less frequently on the face and extremities; on the face, it is more or less limited to the forehead. The spots vary in number from a few up to 600 or 800. The vesicles that appear early are apt to be better developed and more characteristic.

The rash when seen in its early stage of development is a rose-colored macule, which fades away either upon pressure or upon stretching the skin. Its shape is irregular, round, or elongated, and indicates the general contour of the vesicle to follow.

Sometimes large blotches are seen. In a very short time, usually only a few hours, the macule is raised and sufficiently infiltrated to become a papule, but does not have the shotty feeling so characteristic of small-pox. It is superficial, being on the surface rather than deep seated in the skin.

Sometimes these macules do not progress further, so that, in 24 hours, they begin to fade away. Usually, however, they become more or less papular, and remain so for a few hours to a day or two, after which a minute vesicle appears on the top. This vesicle assumes various sizes and shapes, in the course of development. The size varies from that of a pinhead to a small pea, while the shape is globular, ovoid, or elongated. If the vesicles occur in the folds of the skin or in a wrinkle, they are often enlongated and jagged. On the second or third day, the rash can be observed in all its stages, macule, papule, and vesicle, creating the appearance that is quite characteristic of the disease.

The fluid of the vesicle being clear, the distribution of the rash is such as to give the skin the appearance of having been spattered with small drops of shiny water situated on a low maculo-papule. In a few hours or a day, owing to the presence of leukocytes, or (rarely) pus, the vesicle becomes more or less opaque and dries, leaving a small crust yellowish-brown in color.

On the hands and feet, the vesicles appear much less numerous than on the trunk. In these situations, they are invariably small, rather hard, circular and contain only a little fluid.

The vesicles develop on a well-defined pink base, and have a slight areola, which fades gradually. Not infrequently, they rupture, usually from trauma, causing the whole covering to collapse. If only a small part of the contents escapes, or if it is absorbed without rupture, it may leave a center more depressed than the periphery.

In addition, the contents may dry more at the center than at the edges, thus also creating the appearance of a central depression. This aspect is seen most frequently in the unusually large vesicles. These are commonly unilocular; hence it is not the septa, as in small-pox, which causes the umbilication. Sometimes, but rarely, as the fluid contents are absorbed, they contain air, which enter the vesicle through the

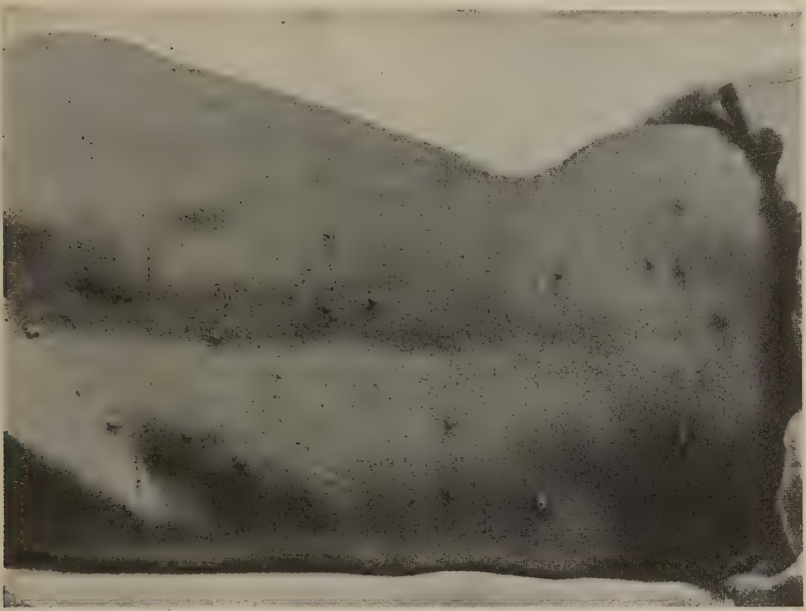

FIG. 25.—Chicken-pox vesicle surrounded by reddish areolæ. (Welch and Schamberg.)

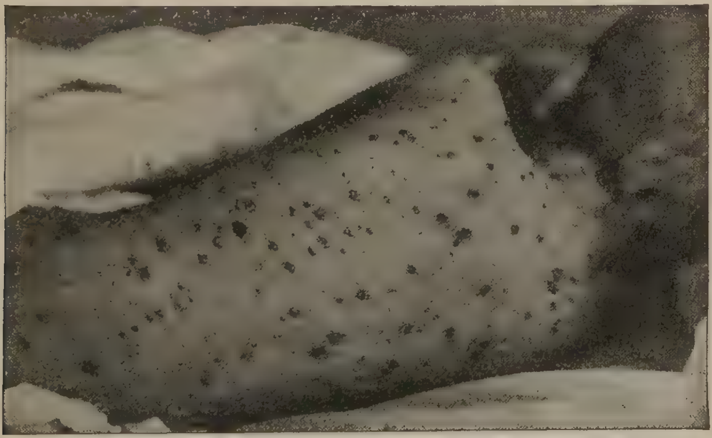

FIG. 26.—Well-marked chicken-pox eruption, showing crusted lesions and recent and old vesicles. Fourth day. (Welch and Schamberg.)

injured epidermis. The top of the vesicle is covered with a thin, transparent, slightly stretched membrane.

The desiccated contents and the epidermis fall off in 5 to 14 days, and leave a superficial, flat, hyperemic or pigmented ulcer, which heals quickly. The epidermis grows in, closes the defect, and the corium returns to its normal condition.

There is little or no scar, unless there has been a mixed infection, as from scratching; then some little pitting may follow. The scar is not foveated, since the true skin has not been involved. The scars, which endure, are more apt to be located on parts particularly liable to irritation, such as the face or trunk.

Not uncommonly, the mucous membranes of the mouth and throat are involved by the rash. In such locations, the vesicles are generally not seen. They develop quickly, usually rupture early, and either give the appearance of small empty blisters with a red areola, or else show small erosions, yellowish-white in color, which are surrounded by a red zone. These may simulate quite closely an aphthous stomatitis. With the throat involved, the cervical glands are apt to be enlarged.

Vesicles on the conjunctiva are rare. When present, however, they cause considerable discomfort, and are sometimes followed by a phlegmon. Much more rare and serious is an involvement of the cornea. Here the inflammation is more marked, and the superficial ulcer, in healing, may leave a permanently blurred spot. Ulcers on the cornea have been reported to extend into the eye, as in small-pox.

Vesicles are found in the auditory canal and in the nose. In the latter, the crusts may impede breathing, and may be associated with bloody purulent discharges. When the crusts separate, considerable hemorrhage may follow.

Vesicles have also been reported at or inside the meatus of the urethra, in both the male and female, where they have caused considerable pain and difficulty in urination. In rare cases, the vesicles may coalesce, or from peripheral enlargement form bullæ. Their crusts may later come away in large masses, exposing raw discharging surfaces. With this local condition, the constitutional symptoms are apt to be severe, and the temperature high. These bullæ may contain blood-stained serum.

Confluent varicella is noted but is rare, and is apt to be associated with some mortality.

Complications and Sequelæ.—These are rare. In the severer forms, albuminuria is present, as it may be in any infectious disease, but the disease itself is so mild that the routine urinary examinations are usually neglected, and its possible presence is not recognized.

Nephritis is even less common than albuminuria. Hemorrhagic nephritis, which has been reported in the literature, has occurred once in the experience of the writer. In his case, the dominant symptom was hematuria with casts. There were practically no signs or symptoms of change of kidney function or of constitutional disturbance. The prognosis of any of the forms of nephritis met with in varicella is good.

Involvement of the serous membranes, such as pleuritis; pleuropneumonia; synovitis of a joint, which is generally polyarticular and involves the large joints, have been reported, but they are extremely rare. If they are present, the effusion is serous, rarely purulent, and the streptococcus is the usual pathogenic agent found.

Abscesses, necrosis of the skin, either superficial or extending into the corium, may follow; these are due to a secondary pyogenic infection of the skin. Erysipelas and impetigo contagiosa may occur. These complications, however, occur mostly in the debilitated, among the neglected poor, or among those living under bad hygienic surroundings.

Hemorrhagic varicella, which has been reported by many writers, is a rare complication. In this condition, the vesicles are usually few in number; instead of clear fluid, they contain blood; and may show a surrounding discoloration, due to the extravasation of blood into the adjoining tissues. Hematuria, epistaxis, or malena may also be present singly or simultaneously. We might expect such a manifestation in a hemophiliac, but this diathesis is not essential, for the condition is due to the intense focal skin infection. Hemorrhagic varicella may manifest itself likewise in another form, that of petechial hemorrhages into the skin, associated with the ordinary vesicular rash.

The constitutional symptoms are usually severe, the high temperature with its concomitant symptoms arising, particularly before the rash appears.

The scabs are dark, and are shed much more slowly than in the ordinary varicella.

This hemorrhagic form may lead to gangrenous areas.

Though the disease is due to a virulent infection, usually occurring in the debilitated, the patients in most instances recover.

Gangrene of the skin may occur in any exanthema, but, in none, with such relative frequency as in varicella. It occurs in the underfed, the cachectic, the tubercular, and in those much depressed from diseases like whooping-cough and catarrhal pneumonia.

The scalp and the trunk are the favorite sites. When gangrene occurs some, though not all, of the spots are more or less suddenly surrounded by large inflammatory areas. The contents of the vesicles become hemorrhagic. Later black crusts form, which, as they come off, leave sharp edged ulcers, punched out in appearance. The floor of this ulcer is covered with pus or small cheesy masses. The ulcers vary in size from that of a small pea to a silver dollar. Their shape also varies, since some of them may fuse together. They vary in number, and the necroses vary in depth, even extending down to the muscles, or to the bone, as on the scalp. The cicatrices left are permanent, and, if on the face, may cause disfiguration.

The constitutional symptoms are naturally severe, and the prognosis grave, for pyemia with secondary abscess eseasily develops.

Gangrene is a condition superadded to varicella, and is not due to the specific infection. Unruptured vesicles are not apt to become gangrenous.

The **prognosis** is as a rule excellent, death being very exceptional. Sepsis is the commonest cause of severe illness. In hemorrhagic varicella, the prognosis is guarded, and in the gangrenous variety is grave.

Prophylactic Vaccination.—Reports on prophylactic vaccination in institution epidemics have been made by Kling and Handrick of Stockholm in 1912 and 1914, by Sophie Rabinoff of New York in 1915, and by May Michael of Chicago in 1917.

Kling made six superficial skin punctures on each child, and inoculated all of them from typical vesicles, i.e., vesicles containing clear fluid seated on a slightly red areola. He stated that in only 5 per cent. of those vaccinated did a reaction appear at all the points of inoculation; in each case, however some one point showed more or less local reaction. This reaction appeared about the eighth day in the form of a vesicle or a group of vesicles, which very soon dried up and left a slight scab. In an institution epidemic, he vaccinated 31 children, only one of whom became ill with varicella; whereas of 64 unvaccinated in the same institution, two-thirds developed this disease.

Handrick as a prophylactic measure vaccinated 127 cases, first by the von Pirquet method, and later by scarification, as suggested by Kling. Thirty-four cases of varicella developed among this number. Thus his results were not as successful as Kling's.

In 1915, Sophie Rabinoff reported unusually good results from prophylactic vaccination. She found that, lues being excluded, direct and immediate transmission, from the vesicle to the child, was the best method. Instead of multiple punctures, she used small scarifications, and used the vesicular contents whether clear or cloudy. In her first series of 50 children she used only one scarification and the local reactions were either very slight or failed to occur. In the second series of 60 children, she made three or four scarifications. In only one did a slight typical reaction occur. In none were there evidences of systemic disturbance.

She formulated her results as follows:

In one ward 38 susceptibles were exposed and 32 developed it.
In another ward 28 susceptibles were exposed and 21 developed it.
In another ward 12 susceptibles were exposed and 10 developed it.
In another ward 20 vaccinated were exposed and 0 developed it.
In another ward 37 vaccinated were exposed and 3 developed it.

Among all her groups there were 142 susceptibilities exposed, of which 114 or about 75 per cent. developed varicella; whereas among 76 who were vaccinated, after exposure to the disease, only six or about 8 per cent. developed it, and these six developed the disesase within the period of incubation of 16 days.

May Michael reported 32 children exposed to the disease who were given prophylactic vaccination. Seven of these developed varicella. Eight of the vaccinated developed local lesions, of which number four later developed the disease. She states that nothing definite can be stated regarding the effect of vaccination on the severity of the disease.

These four reports show that 48 out of 265 exposed children fell ill with varicella even though promptly vaccinated. At the same time, it is indicated that prophylactic vaccination provides some protection and does lessen the spread of the disease.

The great problem in this procedure has been to obtain the virus, for animal inoculations have never succeeded. Further, it is not known how long the virus is active. Rabinoff has never propagated it, while on the other hand, Kling reports to have propagated it through six generations.

I can find no records of trials of prophylactic vaccination with vesicular pulp, as in small-pox.

To be successful, prophylactic vaccination is effective only during the earliest part of the incubation period, and hence must be done, if possible, on the day the first case is discovered in a ward.

The **diagnosis** is usually not difficult. The most important disease to differentiate from varicella is small-pox.

Differential diagnosis of the rashes of:

Varicella	Variola
1. The rash is equally or more abundant on the abdomen and chest than on the face.	1. The rash is more abundant on the face and most scanty on the abdomen and chest.
2. The rash covers the back and abdomen about equally.	2. It is much more abundant on the back than the abdomen.
3. The distribution is indifferent.	3. It is more abundant on the shoulders than across the loins, and on the chest than the abdomen.
4. The rash tends to avoid the limbs.	4. Next to the face, the rash tends to favor the limbs, generally the arms.
5. The rash on the limbs is distributed more toward the trunk than to the extremities.	5. The distribution on the limbs is more toward the extremities.
6. Except on the face, the rash behaves indifferently as regards prominences or surfaces exposed to irritation.	6. The rash favors prominences and exposed areas and tends to avoid protected surfaces, flexures and depressions.
7. The lesions are superficial, and the base is little, if at all, infiltrated.	7. The lesions are deep-seated and have an infiltrated base.
8. The lesions frequently have irregular outlines, and when near a flexure are apt to be oval or elongated.	8. The lesions are generally circular in outline.
9. Are generally unilocular.	9. Are generally multilocular.
10. Are seldom indentated or dimpled.	10. Are generally umbilicated.
11. Evolution of the bleb is complete in three days.	11. Requires eight days.

Differential diagnosis in general of:

Varicella	Variola
1. Incubation 14 days or more.	1. Incubation 12 days.
2. Almost always children.	2. Any age; mostly adults.
3. Period of invasion is usually one day or less.	3. Period of invasion is three days.
4. Early symptoms are mild or absent.	4. Usually severe and characteristic.
5. Maculo-papules felt, but are soft.	5. Papule distinct, shotty feeling.
6. No secondary fever.	6. Has a secondary fever.
7. Temperature rise is slight.	7. Temperature rise is sudden and high.
8. Duration short.	8. Duration long.
9. Not influenced by small-pox or vaccination.	9. Is influenced by both.

In a doubtful case, one may insert the contents of a vesicle into a well-vaccinated person or a well-vaccinated rabbit, and if the disease is variola, it will, within 24 to 48 hours, give an intradermal or a so-called "immediate reaction;" if it is varicella, it will not.

A more certain differential test is the inoculation of the cornea of a rabbit. If the disease is small-pox, the inoculation will give a marked reaction, which may be called characteristic, while, if it is varicella, it will not.

There is confusion, under some circumstances, in differentiating some forms of vesiculareczema, urticaria vesiculosa, impetigo, vesicular and pustular syphilides, and pemphigus, but a study of the case usually defines the diagnosis without question.

If the case is doubtful, it should be vaccinated.

Treatment.—There is no specific for varicella. Prophylactic vaccination can be carried out in institutions, but its efficiency has not yet been sufficiently standardized, or its results sufficiently proven, to make its adoption in general practice worth while in such a mild disease.

The child should be quarantined, not necessarily in bed or indoors, throughout the entire disease until the skin is free from scabs.

As a rule, no constitutional treatment is needed further than quiet and limitation of diet, both regulated according to the severity of the disease. If the child has fever and feels ill, rest in bed for a few days is necessary.

About the most important measure is to guard against secondary infection of the vesicles. To prevent such infection, care of the finger nails and possible restraint of the hands are advisable.

The commonest symptom to require treatment is the itching or burning of the rash. This can be relieved by applying as a protective; plain or carbolized vaseline; olive oil; a solution of bicarbonate of soda containing 1 per cent carbolic acid, zinc ointment, either plain or containing the same percentage of carbolic acid; alcohol and water, equal parts, 5 per cent. to 10 per cent. menthol in pastes or alcoholic solution; vinegar plain or diluted; dusting powders of equal parts of zinc oxide and powdered starch with or without an equal amount of powdered boric acid, stearate of zinc with menthol; 5 per cent. ichthyol in sterile oil, etc.

If these local measures fail to relieve, it may be necessary to use a little bromid or chloral to relieve systematically the discomfort of the local irritation.

The child should have a daily bath, in which friction should be avoided.

If the vesicles become infected, they should be treated with boric acid dressings or fomentations, possibly disinfected with iodin.

If the case becomes gangrenous, supportive measures are demanded.

For the subsequent anemia, good food, plenty of air, and tonics of iron and cod-liver oil are in order.

CHAPTER CXLVII

ASIATIC CHOLERA

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Historical Considerations.—Cholera is endemic in certain areas of India and probably in China, Japan, Java, Siam, and the Philippines. It is also not unlikely that the disease is endemic in certain areas in the Balkans and the nearby Russian territory. Certain it is that in the recent war cholera was frequently conveyed by Russian, Roumanian, and Serbian troops to Austrians and thence to Italians. In the past it has been assumed that the disease has from time to time advanced from India and caused great world pandemics. In the light of our present knowledge it seems more probable that the human cholera carrier is the important reservoir of the disease, and that the inter-epidemic carrier is not necessarily confined to India. Cholera has appeared in America in epidemic form in recent times during five different periods (1830, 1846, 1865, 1884, 1892) and has been more or less continuously present in some parts of Europe from 1910 to 1920. In 1910 cholera was transmitted from Russia to Bari in Italy, and from there it spread through southern Europe. Sparks from this outbreak repeatedly fell into the United States in 1911, but the sanitary defenses of the nation promptly extinguished them. Among the great distributors of cholera are the Mohammedan pilgrims who come from all over the world en route to Mecca. A severe outbreak of cholera began in the Philippines during March, 1902, and continued until April, 1904, during which time there were 166,252 cases and 109,461 deaths. There is considerable evidence to show that the disease prevails in similar epidemic form in Java, the Straits Settlements, Japan, Siam, Indo-China, and to a more limited extent, in China.

Etiology.—Cholera is caused by the vibrio of Koch, although the presence of this organism in the human intestines does not necessarily mean that the individual has or has had cholera. It has now been well demonstrated that many persons harbor cholera organisms but do not have the disease, especially in districts where cholera prevails. Cholera is directly transmissible from man to man. An example of this form of transmission is well illustrated by a doctor or a nurse whose hands become infected with the discharges of a cholera case and who then contract the disease. Great epidemics are probably caused by the water supply becoming infected with cholera infected human excrement. The hands of persons who come in contact with cholera stools and then handle food are probably a great factor in the dissemination of the disease. It should also be remembered that cholera germs can live in water under favorable conditions for more than 100 days, and they have been reported to have remained alive in human feces for a period of 163 days. Cholera spread by the routes of travel. It is important to draw attention to the fact that organisms resembling cholera vibrios are frequently found in human discharges, and that it is only by careful cultivation and agglutination tests that the cholera vibrio can be definitely identified.

Epidemiology.—The old view that cholera persists indefinitely in certain water supplies similar to those of the Ganges is not tenable, although it is well known that the organism may remain viable in certain waters for many months. A river like the Ganges may be continually infected by the human discharges which it receives so constantly from the pilgrims from afar, as well as the people native to its shores, but that does not mean that it is the primary source of the disease. The spread of the disease is always along the line of human travel and it spreads no faster. It is probably carried in the intestines of human beings and perhaps to a lesser extent in the food and water supplies which are used for human consumption. It is primarily a disease of the human intestines and it is probably never contracted except by the introduction of the specific organism into the mouth. Cholera may also be transmitted by animals. In 1914, Barber,[1] of the Bureau of Science in Manila, showed that cockroaches which fed on human cholera feces may harbor cholera vibrios in their intestines, and that they may occur in enormous numbers in the insects' feces for at least two days after the last feeding. Great epidemics occur through the infection reaching the water supplies, and small outbreaks are due to the organisms reaching the food by means of infected hands or by flies or other insects. There is an authentic case on record in which flies transmitted the disease to the nursing bottle of an infant. Cholera is mostly a disease of warm countries, although very severe outbreaks have occurred in countries of the temperate zone, usually in summer when the conditions are tropical. Strictly speaking, cholera cannot be said to be a race disease, although in Manila, for instance, the statistics show that one Chinaman out of 7000 contracted the disease, whereas one Filipino out of 300 contracted the infection. This is probably due to the personal habits of the two races. The Chinese practically never drink water except in the form of boiled tea, and they eat food with chopsticks. The Filipinos drink unboiled water and eat food with their fingers, thereby affording an excellent opportunity for a cholera carrier to transmit the infection to the common bowl which serves so frequently as a receptacle in which two or more persons dip their fingers to partake of food.

Pathology.—Until quite recently it was believed that the cholera organisms could be found only in the intestines, and that the symptoms and effects of the disease were due to the production of an endocellular toxin. Greig[2] has lately demonstrated the presence of the cholera vibrio in the spleen, but up to the present time it has not been possible to state whether the vibrios outside of the human intestines are connected with the symptomatology. In general, however, it may be stated that the vibrio is found abundantly in the glands, epithelial cells, and the mucosa of the small intestines. It is presumed that an endotoxin which is set free causes the gastro-intestinal disturbance which is responsible for the passage of fluid from the blood into the bowel. Analyses show this at first to consist of water, then sodium chlorid and other organic salts, still later phosphate and potassium salts, and finally organic substances. The fact that water is found first would indicate that the process is not an endosmosis. It may be a secretion. At all events it causes great concentration of the blood, the specific gravity reaching 1078. In the concentrated form sometimes as many as 8,000,000 red corpuscles per cubic millimeter are seen. There is a marked fall in the blood pressure, which may be as low as 50 mm. of mercury. The secretion of urine is generally suppressed or scanty, with high specific gravity, albumin, casts, and an increase in the amount of indican.

Morbid Anatomy.—As a rule the post-mortem rigidity is marked. It sometimes happens that bodies dead of cholera change position; sometimes they rise to a sitting posture or are thrown from the table by severe muscular contractions. Occasionally contractions which force air out of the lungs produce sounds which strike terror into the hearts of those who are not familiar with the cause of their production. On cutting the tissues it is noticed that they are very dry, and that the blood is frequently thick and tarry in appearance. On opening the peritoneal cavity a sticky sensation is imparted to the hand when it is passed among the loops of the intestines. This is usually very characteristic and is peculiar to cholera. The stomach nearly always contains fluid, and when death has been sudden it may contain food. The intestines are reddish in appearance and there are often small punctiform hemorrhages. The reddish appearance, however, is not specially characteristic, and is much the same as seen in other conditions. The contents of the intestines are usually found to be a whitish turbid liquid very much like the whitish-gray translucent sauce commonly used for cottage pudding, but somewhat thinner. It often contains small flakes of whitish appearance. On microscopical examination these are found to consist of food particles, epithelial cells, blood corpuscles both red and white, mucus and microörganisms. The mucosa of the stomach and intestines is generally hyperemic and swollen, and may be marked with numerous punctiform hemorrhages. The villi are swollen, giving the surface a dull opaque translucent appearance, and Peyer's patches and the solitary follicles are much enlarged. The ilium and the upper end of the large intestine appear to be studded with cooked sago-like grains. In the lower bowel there are usually large quantities of the turbid whitish fluid described above, but if death has been due to cholera sicca the stools are usually hard and firm and even cholera flakes are rare. The glands of the stomach and duodenum are enlarged and the surface is denuded of epithelium.

There are no special lesions of other organs. The liver is seldom enlarged and only rarely does it show moderate cloudy swelling. The spleen is usually normal, but may be small, hard, and wrinkled upon its surface and deep red upon section. The kidneys have a characteristic deep red and opaque appearance, this change being most marked in cases in which anuria was present some days before death. The heart is usually soft and flabby, with muscle degeneration. In cases in which death has been rapid there are frequently ecchymoses on the surface of the endo- and pericardium. Cholera pneumonia is often present in cases which have been ill over three days. Cholera vibrios are present in Lieberkuhn's follicles, in the epithelial cells, and in the mucosa of the intestine and the stomach. Rebulski and Greig[3] have recorded cases in which vibrios were found in the liver, spleen, and heart.

Spirillum of Cholera.—The cholera vibrio was discovered by Koch[4] in 1883 in Egypt, and he confirmed his work the following year in India. In the intestines and dejecta the organism presents the appearance of a short, thick rod slightly curved in the long diameter. It is about half as long and twice as thick as the tubercle bacillus, being 0.8 to 3 microns in length and 0.3 to 0.5 micron in breadth. It is generally found singly, but it may be arranged in pairs with the curves opposite each other, in which event it may resemble the letter S. A simple microscopical examination of a smear preparation is not sufficient to establish a diagnosis or to exclude a diagnosis. It often happens that curved organisms cannot be found in smear preparations, but they may be recovered by culture. The motility is very characteristic and has been demonstrated by Loffler to be due to fine celia which are longer than the bacteria and are attached to one end of the organism. Many different methods for the bacteriological diagnosis of cholera have been devised. The method used by Schobl and other workers (used many thousand times at the Bureau of Science in Manila) has proved reliable, quick, and practical. It may be described as follows: "The stool specimen, which is collected with a sterile glass tube, is placed into a tube containing a slightly alkaline 1 per cent. peptone solution. This is incubated for some 12 to 20 hours and then transplanted to Dieudonnes plates. On these plates practically no other organisms are found except those of cholera, and the growth of the cholera organisms is characteristic. A small amount of culture is then taken from Dieudonnes plate and brought in contact with the cholera serum, and the coagulation may easily be observed by the naked eye, and the characteristic clumping may be seen under the microscope." In making examinations of cases of cholera which occur in places where laboratory methods are not immediately available, it has been found that if stool specimens taken with sterile glass tubes are placed into agar tubes, the organism may be recovered from such transplants up to five days from the time the specimen was taken. In the Philippines these tubes are kept at ordinary temperatures, usually ranging from 26.7 to 35°C. (80 to 95°F.). They may be mailed in ordinary mailing tubes. Schobl,[5] in 1914 in Manila, found that the cholera organisms live for six days in distilled water, 33 days in ordinary Manila tap-water, and over 106 days in sea water. Certain food may be of great importance in transmitting the organism, as in the case of milk, in which it grows without producing any visible alteration. It has been shown that the organism would live for at least two days in milk and 48 days in butter. According to Koch, a solution of 1:400 of carbolic acid, 1:25 of sulphate of copper, and 1:10,000 of corrosive sublimate is sufficient to arrest development. Ashburton[6] has shown that creolin, 1:2000, destroys the vibrio. The cholera organism has but feeble resistance to drying and to sunlight; it is easily killed with a weak germicidal solution. In general, it may be stated that the organism will not remain alive in ordinary drinking water for more than six to seven days.

Symptomatology and Course.—The outstanding picture in cholera is the violent purging, vomiting, muscular cramps, suppression of urine, husky voice, and collapse. Cholera may have an incubation period lasting from two to five days, but in the great majority of cases it is not over 48 hours. The cholera conference at Constantinople concluded as follows: "That all the facts cited in regard to a period of incubation longer than a few days are based upon cases that are not conclusive, either because the premonitory diarrhea was comprised in the period of incubation, or because the infection could have occurred after the departure from the infected locality." It quite frequently happens that the appearance of the first cholera symptoms is preceded by prodromata in the form of diarrhea or a feeling of malaise. As a rule the onset is sudden. The attack usually begins with diarrhea and colicky pains in the abdomen. Vomiting generally occurs later. At first food is vomited and this is followed by watery fluid with bile and occasional blood. The stools at first are formed in character, but soon assume the so-called rice-water appearance with numerous white flakes, which, when examined, are found to consist of mucus which contains vibrios and epithelial cells. Sometimes blood is passed, but this is rare, and may be due to hemorrhoids or other local cause. The thirst becomes severe. As the purging and vomiting continue the urine diminishes and suppression usually follows. The blood leaves the subcutaneous tissues, contractions of the limbs are common, with severe cramps in the muscles; the facies alters, the nose becomes sharp, the cheek-bones prominent, the eyes sunken, the skin of the fingers wrinkles like those of a laundress. Similar wrinkling takes place about the feet. The circulation is profoundly affected; the systolic blood pressure falls, often varying from 20 to 60. The pulse becomes quick and rapid, the heart sounds diminish, the lips pale, the nails become bluish, the respiration is rapid, and the voice characteristically husky. The mind is generally clear; the patient is apathetic except during the agony produced by the severe cramps. The skin feels cool and clammy, and the axillary temperature falls below normal, although the rectal temperature may be above normal. The patient quickly passes into the second stage of the illness and unless improvement takes place, the so-called algid stage comes on. The pulse disappears at the wrist, the heart sounds become weak and irregular, the bladder empty. The diarrhea ceases and the patient becomes comatose, and death supervenes from 12 to 36 hours after the onset of the attack. If the patient is to recover, the diarrhea diminishes, the skin becomes warmer, the pulse and blood pressure improve, the kidneys secrete, the subcutaneous tissues gradually absorb a normal quantity of fluid, and the appearance of the patient gradually returns to normal. Probably the most favorable symptom is the reëstablishment of the renal secretion. Cases sometimes recover in which there has been a complete suppression of the urine for more than 72 hours. Cholera is frequently spoken of as occurring in the following varieties:

1. Ambulant cases, which also include cholera carriers who show no symptoms of the disease except the presence of the cholera vibrios in the stools.

2. Choleraic diarrhea, characterized by severe purgation and the passage of yellow stools which contain cholera vibrios. Recovery may take place before the patient passes into a typical attack of the disease.

3. Cholerine, characterized by sudden abdominal pains, numerous feculent stools followed later by rice-water stools which last for about a day, with recovery of the patient without further symptoms. True cholera organisms are not found in these cases.

4. Cholera sicca, a rapidly fatal form of the disease, in which death occurs before the typical symptoms of diarrhea and vomiting appear. Bacteriological examination of the stools shows cholera vibrios almost in pure culture. In this type of cholera it sometimes happens that persons are stricken while walking on the street; they suddenly fall to the ground and often die before assistance can reach them. Persons are sometimes seized in the night and are found dead in bed in the morning.

In brief, the prominent symptoms in typical cholera may be summed up as subnormal temperature in the axilla, husky voice, severe cramps in the legs and arms, suppression of urine, whitish, turbid fluid stools, absence of fluid in the tissues, cool, clammy, profusely perspiring skin, and thready pulse. These make a combination never to be forgotten by those who have seen the disease. The temperature often falls to 35°C. in the mouth.

Duration of the Disease.—The duration of cholera may be divided into three stages. First, the stage of invasion, during which there is great evacuation lasting from a few hours to a day. Second, the stage of urinary suppression lasting from the second to the fifth day. In rare instances it may extend several days longer. Third, the stage of reaction or death, which may begin after the first 24 hours. The common period is the third day.

Complications and Sequelæ.—The most common complication is pneumonia. Nephritis is often given as a complication, but it should be regarded as part of the disease as it is one of the most constant lesions. At times gangrene of the lungs may occur. Abortion in pregnant women is the rule. Extreme anemia, tendency to diarrhea, and digestive disturbances may persist for a long time. Cholera is seldom followed by sequelæ. Usually restoration to health is complete. As a rule the damage which has been done to the kidneys undergoes complete repair. Occasionally intestinal symptoms similar to those of gastritis and intestinal catarrh may follow an attack of cholera, but these disappear in the course of time.

Diagnosis.—The diagnosis of cholera during the presence of an epidemic is very simple, but the first cases of an outbreak are frequently overlooked. However, the following symptoms should always lead to a careful bacteriological examination of the stool for cholera vibrios. Cases of sudden illness in which there is vomiting and purging, subnormal temperature, suppression of urine, clammy perspiration, husky voice, severe cramps in the arms and legs (especially in the calves), weak thready pulse, wrinkling of the skin of the hands and feet, should be tentatively regarded as cholera.

Prognosis, Mortality in Childhood.—At the beginning of an outbreak the mortality is often as high as 90 per cent., whereas toward the end of an epidemic the mortality may fall to 15 per cent. A fair average mortality in an epidemic is about 50 per cent. Probably the large amount of conflicting evidence as to the value of different treatments for cholera may be explained on the ground that the remedies were given at different periods of the epidemic. A treatment that at the beginning of an outbreak appeared to have no great value might apparently give good results when used by another observer toward the close of an epidemic. Outbreaks occur which are confined almost entirely to children. No satisfactory explanation of this phenomena is available. Much work has been done to trace the infection to food or water which is common to children, but without result. Judging by the writer's experience, the incidence and death-rate among children are about the same as among adults.

Prophylaxis, Vaccination against Cholera.—Two principles govern the measures which should be taken to avoid cholera. The first looks to the exclusion of living cholera spirilla from the gastro-intestinal tract. The second consists in preserving and adding to any natural resistance which may exist. According to the available statistics, the vaccins developed against cholera during the past few years are proving of value. Sensitized vaccin was used in the inoculation of 238,000 people in Tokyo.[7] Of the uninoculated, 1.85 per 10,000 contracted cholera, and only 0.13 of the inoculated. In another group of 62,000, of the uninoculated 3.09 per 10,000 contracted cholera, and 0 of the inoculated. Similar experiences were had with Italian soldiers and among large numbers of people vaccinated in Java, the Philippines and Sumatra. It is believed that the toxins produced by the cholera spirillum are not absorbed through intact intestinal epithelium, but gain entrance to the circulation only after the epithelium has become damaged, necrosed, or desquamated. Therefore, all dietary indiscretions which might cause intestinal irritation are to be avoided. Over-fatigue and exposure to cold are to be carefully guarded against. But it appears wise not to change suddenly the ordinary mode of life, but to follow the usual habits in a temperate manner. Care in the character of the food is important. All articles which might carry infection should be avoided entirely, or eaten only after being cooked, and while they are hot. This is especially the case with water and milk, which should be heated to the boiling point. Prolonged boiling is not necessary, but to insure the death of the spirillum it is safest actually to boil liquid articles of food. As a prophylactic measure it has been recommended to take acid drinks such as very weak hydrochloric or sulphuric acid. But it seems doubtful whether this is a wise procedure, in view of the danger of disturbing the digestion if sufficient acid be taken to act as an effective agent in killing the spirillum. Furthermore, there is also the objection that the use of these acidulated solutions over a period of several days there may be interference with the hydrochloric acid and other gastric secretions, injury to the intestinal mucosa which may break down natural defenses, and thus make the danger greater than if such solutions had not been taken. Particular care should be observed by those attending cases of cholera. They should disinfect the hands immediately after they have come in contact with the dejecta or vomitus from the patient. A 2 or 3 per cent. solution of carbolic acid, 1:1000 solution of mercuric chlorid, or 1:1000 solution of bichlorid of mercury, may be used for this purpose. Chlorid of lime solutions are not desirable, owing to the fact that no dependability can be placed upon the amount of chlorine which they may contain. Success in preventing the spread of cholera depends solely upon the destruction of the spirilla, and this means the safeguarding of the entire human excreta of any community in which cholera appears. A campaign against cholera resolves itself into disinfecting or otherwise safeguarding human excrement. In North American cities this is largely accomplished by the water carriage of sewage which is the custom almost everywhere, so that a serious cholera epidemic is almost impossible. The next important step is to safeguard the water supply. Even in the case of water supplies that are derived from uninhabited watersheds, it is believed now to be strictly indicated that all such supplies should be safeguarded by the introduction of calcium hypochlorite in quantities which have been determined by an expert to be suitable for the water to be treated. A solution of 1:3,000,000 in water which contains little organic matter is sufficient. Cases of cholera should be promptly isolated and placed under the care of competent persons, so that the stools and vomitus may be promptly disinfected, as well as all materials with which they may have come in contact. For this purpose 5 per cent. carbolic acid solutions used in two or three times the bulk of the material to be disinfected is perhaps the most reliable and efficacious disinfectant, although many of the coal tar derivatives may be used if carbolic acid is not available. All contacts of cholera cases should be promptly examined in order to determine whether they are cholera vibrio carriers, and if found infected should be isolated the same as cholera cases. Places where cholera cases are kept should be strictly safeguarded against flies because there is great danger of spread from this source. Another common means of spread is by the hands of individuals who have assisted persons who have been stricken with cholera and who do not realize that they may have become infected. It is no longer necessary to place quarantine upon merchandise because many practical experiments have shown that even in articles which are usually contaminated it is impossible for the cholera organism to live for more than five days except in a water supply. The dead should be wrapped in wet bichlorid cheets and placed in hermetically sealed coffins to guard against the discharges leaking therefrom before the body reaches the grave or is cremated. In brief, the measures to apply in any given community in which cholera appears will readily suggest themselves to any sanitarian when he remembers that the whole question resolves itself into the prevention of human excrement from cholera cases or carriers from reaching the mouths of human beings, and that in order to be certain that this does not happen, the human excrement of the entire community must be safeguarded.

Symptomatic Treatment.—The great number of remedies advocated for cholera probably gives the best evidence that no satisfactory treatment has been found. After an experience with many thousands of cases, it may be stated that the following treatment probably produces as satisfactory results as any other: The patient is placed in a warm bed with artificial heat, which may be supplied by hot blankets, hot-water bottles, or electric warming pads. The guide to the amount of heat necessary is a normal axillary temperature. A preliminary dose of $\frac{1}{2}$ gr. (0.03 gm.) of calomel often seems of service. Fluid by mouth is given freely. Vomiting is a more or less constant symptom, and the use of water, which is of value in cleaning the stomach, does not seem to increase it. A certain amount at least is absorbed and perhaps aids in the elimination of toxins. Intravenous injections of normal salt solution are given at intervals of a few hours in quantities sufficient to produce a full pulse. The quantity required to do this in an adult is usually from one to two liters (quarts). In the course of 24 hours five liters may be necessary. A stimulant like strychnin, in $\frac{1}{60}$ gr. doses, is usually necessary. Morphine is given in sufficient amount to make the patient comfortable. The treatment with strong alkaline salt solution, advocated by Rogers,[8] has not given any better results at the San Lazaro Hospital in Manila than ordinary salt solution. Any measures which will induce the skin to take over the work of the kidneys should be employed. By actual experience it has been determined that in all cases in which there is no marked suppression of urine, the patient will generally recover without any treatment whatsoever. From time to time remarkable claims are made for the therapeutic efficiency of the bolus alba or Fuller's earth treatment. For instance, Kuhne[9] claims to have reduced the mortality from 45 per cent. to 2 or 3 per cent. The method he employs is to mix equal parts of water and bolus alba (kaolin). A glassful should be taken every hour. It is seldom necessary to take more than six glasses (about 200 gm. of kaolin) in the first 12 hours. After that it is given symptomatically. The patient, it is claimed, can leave the hospital within three days.

Serum Treatment.—During the past 20 years efforts have been made to produce a serum for cholera. Much work was done in Germany and India. The French also have given much attention to the question. The French Colonial Officers in Indo-China thought for a time that they had been successful, and came to the Philippines to give the serum a trial on a large scale. The results were wholly unsatisfactory and statistically not as good as were being obtained in the same out-break with ordinary symptomatic treatment described above. In brief, it may be stated that up to the present time there have been no reports published of any serum that will yield as satisfactory results as the intravenous injections of salt solutions.

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CHAPTER CXLVIII

INFLUENZA

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Definition.—Influenza is an acute infectious pandemic disease caused by the entrance of the Influenza Bacillus into the human body. It is characterized by fever, more or less prostration, and by inflammation of the respiratory and the gastro-intestinal tract. Although the term influenza or grippe should really be restricted to those cases which have been definitely proven to be due to the Influenza Bacillus, described by Pfeiffer in 1892, nevertheless identical symptoms and signs can be caused by a variety of other organisms, such for example, as the streptococcus, pneumococcus, micrococcus catarrhalis, etc. According to the majority of recent observers, it is impossible to tell by clinical symptoms alone to what organism the "infectious cold" is due. Inasmuch as the influenza bacillus can as a rule, only be isolated in hospitals with good laboratory facilities, an accurate diagnosis must necessarily be limited to hospital cases alone. We agree with Forchheimer who maintains that all widespread epidemics of "colds" should be looked upon as influenza.

History.—Although epidemics of influenza have been described in the very earliest times, the name influenza was first given to the disease by Pringle and Huxham in the epidemic of 1743. The name grippe also originated at about the same time. It was called grippe in France and Belgium, and influenza in Germany and other countries. Had the bacillus been discovered in France instead of in Germany, it would not doubt have been called the bacillus of grippe instead of the influenza bacillus.

The first great pandemic of influenza occurred in 1510. According to Finkler, the disease at that time spread all over Europe. Brought to Sicily from the Island of Malta, it invaded Spain, Italy, Hungary, Germany, France, and England. Numerous epidemics have been reported since that time. In America the first recorded epidemic occurred in 1627. During the past century, there were four pandemics, 1830-1833, 1836-1837, 1847-1884, 1889-1890; but the disease attracted little attention until the great epidemic of 1889-1890. Since 1890 the disease has appeared in America every winter to a greater or less extent, the most severe epidemic having been in the late summer and fall of 1918, and in the winter and spring of 1919.

Etiology.—It has generally been agreed that influenza is caused by the influenza bacillus, which was first described by Pfeiffer in 1892, and which bear his name. There have, however, been occasions in recent years, especially in America, when observers have failed to find this organism in cases which have had the typical symptoms and signs of influenza. For example: In an epidemic, closely resembling influenza which occurred in America in 1916, the influenza bacillus was very infrequently found. Instead of the influenza bacillus, the streptococcus and the pneumococcus were isolated in many cases. Recently some investigators have maintained that influenza might be due to a filtrable virus. Olitzky and Gates of the Rockefeller Institute have cultivated from nasal secretions a filterable organism which they have called Bacterium Pneumosintes. Until, however, absolute proof is at hand of some other etiological factor, it seems best to consider the influenza bacillus as the cause of this disease.

The Influenza Bacillus is a very small, short, rod, non-motile, Gram-negative, and aërobic. It does not form spores. It stains poorly with the ordinary anilin dyes. Good results are obtained by staining with a weak carbol-fuchsin solution. Smear diagnosis of influenza is unreliable. Cultures must be employed, and even then it is very difficult to isolate the influenza bacillus. It grows only in the presence of hemoglobin. The best medium for its cultivation is blood agar, which was used by Pfeiffer. Colonies in the form of small circular dots appear in 24 hours when incubated at 37°C.

According to Wollstein the real habitat of the influenza bacillus is in the bronchial secretions, where it may persist for many months. Wollstein found the influenza bacillus in the bronchial secretions in 70 per cent. of "suspicious cases" in children. She found it only once in the discharges from 25 cases of otitis media. Inasmuch as the influenza bacillus is most commonly found in the lower respiratory tract (trachea, bronchi, and lungs), and seldom in the naso-pharynx and ears, smears should be made directly from the bronchial secretions, and not from the discharges from the mouth and nose. As infants and young children, as a rule, do not cough up any sputum this procedure is a rather difficult one. According to Holt the best way to procure secretions from the bronchi is by tickling the pharynx and catching upon a swab any secretion brought up from the bronchi with the cough. The bacilli are usually found in the small masses of greenish-yellow sputum. The organism is rarely found in the blood. When it does occur in the blood, death usually results. Animal inoculation with the influenza bacillus has been almost uniformly unsuccessful, the monkey alone being susceptible to infection (Cecil). The influenza bacillus usually dies after a few hours drying in the air.

Influenza is one of the most highly contagious diseases in existence. It spreads with great rapidity. During numerous epidemics, 50 per cent. or more of the population have been attacked. According to many observers one attack of influenza seems to confer immunity to the disease. It was formerly thought that infants were immune to influenza, but this belief has not been substantiated in recent years.

In infant asylums and in hospitals, influenza may spread through whole wards and infect all or nearly all of the infants.

The influenza bacillus is at times found in the nose and throat of healthy persons, the so-called "influenza carriers." In this connection it is interesting to note that Lord found the influenza bacillus in the sputum of three patients two and one-half years after the initial attack of the disease. According to Park, 50 per cent. of the population harbor the influenza bacillus in winter.

Influenza usually arrives with the cold, damp weather. As a rule, it makes its appearance in October, and is present until May.

According to Doty, improper ventilation, overheating of homes, carelessness in dress, and direct exposure such as wet feet and the like, particularly when they are associated with a weakened resisting power of the body, constitute the most common factors in the propagation of influenza. The disease is usually transmitted by direct contact from one individual to another by coughing, sneezing, and expectoration. Infants and small children are very often infected by their nurses or mothers.

Pathology.—There are no pathological lesions characteristic of influenza. Almost any organ or tissue of the body may become involved either by the influenza bacillus itself or by its secondary invaders. It should be borne in mind that at times, in influenza, all local signs of inflammation may be absent. When inflammations are present they do not differ in any respect from those due to other organisms. As a rule, there is present an acute catarrhal inflammation of the mucous membrane of the respiratory tract. The naso-pharynx, trachea, bronchi, and lungs may become involved. There may occur an inflammation of the tonsils, adenoids, middle ear, and accessory sinuses. Dacrocystitis and conjunctivitis may occur. The neighboring lymph glands are often congested and inflamed. In young children and especially in infants, the mucous membrane of the intestinal tract is usually the site of inflammation. At times the nervous system becomes involved. In children the inflammation of the lungs is usually of the bronchial type, but the lobar form of pneumonia is not at all uncommon.

Symptoms.—*The period of incubation* is short, varying from two to four days the most frequent interval being about 48 hours. *The onset* of the disease is usually acute. There is no known infection which presents such a great variety of different symptoms, and in which there are such varied physical signs. Any organ or tissue of the body may become involved.

Based on the most prominent symptoms which are present in the individual case, the following four types of the disease are usually recognized: (1) *Respiratory;* (2) *nervous;* (3) *gastro-intestinal;* (4) *febrile.* At times, however, in certain epidemics, cases have shown symptoms embracing all four types of the disease.

The four types of influenza have certain symptoms more or less in common. In older children the symptoms are very much the same as in adults. In younger children and in infants, the onset, course, and end results of the disease are often more severe than in adults. A good deal depends, however, upon the individual resistence. The disease may begin with convulsions, with chilly sensations, or with a real chill. Prostration is one of the most constant symptoms. There may be nausea and vomiting. Usually there is anorexia. A catarrh of the naso-pharynx is commonly present. The primary seat of infection is usually the throat. More rarely the nose is involved first. From the naso-pharynx the infection may spread to the trachea, bronchi, and lungs. In infants the middle ears are always more or less congested. Conjunctivitis and edema of the eyelids are common. Sneezing is frequent. Very often a troublesome cough is present strongly resembling pertussis, except that no whoop accompanies the cough, unless the patient has recently had pertussis.

Fever is a constant symptom. The type of fever varies greatly. In mild cases it rises to 101 or 102°F., remaining at that height for two or three days with slight morning remissions, and then gradually dropping to normal. Often it is higher in the morning than in the evening. In the more severe cases the fever may reach 105 or 106 degrees, and may fluctuate greatly. It may continue high for a few days, and then gradually or abruptly drop to normal. At times the fever curve is strongly suggestive of sepsis; at other times it may resemble malaria. In some cases which I have observed, the morning remissions have been as much as 10 degrees, the temperature varying morning and evening between 96 and 106 degrees respectively. This type of fever may continue for several days. In some cases the temperature may remain elevated for several weeks, and strongly suggest typhoid fever, especially as the spleen is often enlarged in influenza. At other times cases are seen with intermittent temperature, which may continue for months, and strongly suggest tuberculosis.

Accompanying the fever there is a feeling of malaise. Older children complain of pain in the muscles of the extremities and back. At times there is headache and delirium. At other times apathy. Eruptions of the skin in the form of an urticaria or erythema, which at times resembles scarlet fever or measles, are not uncommon. Herpes is occasionally seen. Albuminuria is present in about 10 per cent. of the cases, usually in those with high temperature and toxemia. The albuminuria disappears shortly after the temperature has dropped to normal. Real nephritis is rare. The blood in uncomplicated cases of influenza usually shows a leukopenia. This may even persist in the presence of pneumonia.

As a rule, influenza runs its course in from three days to a week. The more severe cases however, may last for weeks or even months.

The Four Types of Influenza.—The **respiratory type** is by far the most common form of influenza. Any part of the respiratory tract from the naso-pharynx to the lungs may be attacked. There may be coryza, tonsillitis, pharyngitis, adenoiditis, laryngitis, tracheitis, bronchitis, or pneumonia. Epistaxis commonly occurs. Often the middle ear, the mastoid cells, and rarely the accessory sinuses are involved. An enlargement of the cervical glands is often seen. In the mild cases there is present a simple coryza with sneezing, slight muscular pains, and perhaps malaise and prostration. The temperature varies between 100 and 102 or 103°F. These symptoms last only a few days, and if there are no complications, complete recovery soon occurs.

In the more severe cases, there follows an involvement of the lower air passages. There may be present a mild grade of bronchitis affecting the larger bronchi, or a more severe form involving the finer bronchi with a resulting so-called "capillary bronchitis." When this involvement occurs, the temperature rises to 104 or 105 degrees. There is marked prostration and at times delirium, cyanosis, dyspnea, and perhaps asphyxia are present. When the cyanosis is associated with a marked pallor the prognosis is usually very unfavorable. There may be a very troublesome cough which makes the young patient very uncomfortable. Not infrequently an inflammation of the lung follows the involvement of the finer bronchi. This is caused either by the influenza bacillus itself, or more commonly, by one of its secondary invaders. The pneumonia is usually of the lobular type, but lobar pneumonia is very often met with in children, and even in infants. Empyema may result, which in young children is always a serious condition, and in infants is almost always fatal. The temperature in influenza pneumonia rarely falls by crisis. The temperature may be intermittent for days and weeks, and the signs in the lungs may persist, so that one is almost certain that an empyema is present. Often in this class of cases, the chest is punctured again and again without result. Finally, in the favorable cases the signs in the lungs clear up, and the temperature remains normal. Convalescence is usually prolonged, as weakness and prostration persist for some time. In this connection, it is of interest to mention a case reported by Lord and cases observed by the author in which the bronchial breathing disappeared only after a period of months.

The **nervous type** of influenza is very common in young children. Catarrhal symptoms in this type are usually very mild in character. Occasionally however there is a complete absence of such symptoms. At times a combination of catarrhal and nervous manifestations are seen. Headache is a very prominent symptom. Severe pains throughout the entire body are a prominent characteristic of this type of influenza. Convulsions frequently occur, some of them very severe in nature. Great prostration is of frequent occurrence. Restlessness, irritability, insomnia, delirium, apathy or even coma are not uncommon. The temperature is usually high (105 to 106), but it may be of moderate grade (102 to 103) with very marked nervous symptoms. Severe cerebral symptoms simulating meningitis may occur. Cases of so-called serous meningitis or meningism, with fever, headache, vomiting, delirium, opisthotonos, a positive Kernig reaction, tache cerebrale, and other signs of meningitis, with a spinal fluid which is under considerable pressure, but which is water clear, and which gives a negative bacteriological and chemical examination, are at times encountered, and have often caused mistakes in diagnosis. Purulent meningitides, in which the influenza bacillus has been found in the exudate, have been reported. These cases are nearly always fatal. Encephalitis causing hemiplegia and monoplegia may occur. Neuritis is rare in children.

The **gastro-intestinal type** of influenza occurs mainly in young children and infants. Frequently in this type there are no signs referable to the respiratory tract. With the sudden rise in temperature there is nausea and vomiting. The tongue is coated, and there is complete loss of appetite. At times abdominal distress rising to severe abdominal pain is present. It should be borne in mind that children affected with the respiratory type of influenza, also complain frequently of abdominal pain. Upon close investigation, however, it will be found out that this pain is usually muscular. According to Brenneman enlargement of the mesenteric glands may be the cause of abdominal pain. True abdominal pain is most frequently encountered in combination with other abdominal symptoms, such as tympanitis, rigidity of the abdominal muscles and diarrhea. The diarrhea may be very profuse. Mucous, bloody, watery stools are not infrequent. Collapse may occur. Occasionally jaundice is present with slight fever, constipation, an enlarged and tender liver, and a palpable spleen. This class of cases with the symptoms of "catarrhal jaundice" are often found in epidemics. Several cases may occur in the same families. Ward epidemics are not infrequently encountered. The temperature remains elevated for two or three days or even longer. The jaundice, which is usually not very severe, persists for a few days or weeks. Some cases of influenza in which there is fever, apathy, delirium, and gastro-intestinal symptoms with the presence of an enlarged spleen, are frequently confused with typhoid fever.

In the **febrile type** of influenza there is very often no localization of the inflammatory process, and the only manifestations of the disease may be fever and more or less prostration. The type of fever is variable. It may be of a continued type, but generally it is remittent or intermittent. At times, the fever lasts a few days or weeks, with but slight nervous symptoms. The face is flushed, and there are chilly sensations or real chills. This type of influenza at times simulates typhoid fever, malaria, or septicemia.

Chronic Influenza.—In the vast majority of cases, influenza runs its course within a few days or weeks, at the end of which time the patient is up and about again. In a certain number of cases, however, relapses occur, and a condition results which has been called chronic influenza, and which at times is very difficult to differentiate from tuberculosis. The temperature, which has dropped to normal, rises again, and for many weeks, months, or even years, may vary between normal or subnormal and a slight elevation (101 to 103 degrees). In children, as a rule, frequent attacks of coryza, pharyngitis, and tonsillitis occur. There is present headache, anorexia, malaise, and irritability. The patients lose much weight and strength, so that they become anemic. Often there is a persistent nagging cough resembling pertussis. Enlargement and at times suppuration of the cervical and other lymphatic glands take place. The bronchial glands may become enlarged and thus become the cause of the persistent cough. Joint pains are at times complained of. In the more severe cases there is found a local or diffuse bronchitis. Localized areas with the physical signs of lung consolidation may be present, and may persist for many months. In the very unfavorable cases interstitial pneumonias, bronchiectases, and lung abscesses are encountered. At times there is profuse expectoration tinged with blood, or containing considerable amounts of it. These cases closely simulate tuberculosis, but their course is more favorable. They may harbor the influenza bacillus for many months or years. According to Lord, death results from pneumonia or some intercurrent disease. At times tuberculosis may develop during the course of influenza, and thus both diseases may be present in the same individual.

Influenza in Infants.—Not many years ago it was thought that infants were immune to influenza. In recent years, however, it has been shown very definitely that such is not the case. In hospitals and in institutions, influenza may infect the inmates of entire wards, and cause as high a mortality among the infants as one sees in the course of so-called "summer diarrhea." Pfaundler's assertion that infants enter hospitals with nutritional disturbances and die of respiratory diseases has only too often been substantiated.

As a rule, influenza runs a much more severe course in infants than in older children. A good deal of course depends upon the individual resistance. A normal healthy breast-fed infant for example, generally does not suffer as severely as a poorly nourished, bottle-fed baby.

The mild cases of influenza in infants resemble very closely the type described in older children. In the more severe cases, the disease may be ushered in with convulsions and a sudden rise in temperature to 105 or 106 degrees. Coryza and an inflammation of the pharynx are present in practically every case. The middle ear also is nearly always involved. Often it is only slightly reddened, and resolution takes place in a few days. At other times pus forms, and the discharge from the ear may last for a long period. Gastro-intestinal symptoms, such as anorexia, vomiting, abdominal pains, and diarrhea are usually present. The stools may be very loose and watery, and may be composed chiefly of mucus, pus, and blood. The abdominal distention may be so intense as to simulate peritonitis or intestinal obstruction. The anorexia combined with the persistent diarrhea may be so severe as to cause marked loss in weight and even collapse in very little time. Irritability and great prostration may occur. Respiration may be difficult and sleep much disturbed. Cyanosis is frequently present. The heart is often very weak, and the pulse rapid. The most commonly observed temperature in infants is that which rises slightly in the evening, and is almost normal in the morning, but it should be born in mind that no form of temperature is typical in influenza. In weak, premature babies and in poorly nourished infants it is not uncommon to observe normal or subnormal temperature during the entire course of influenza. even where there is marked pulmonary involvement. The larynx, trachea, bronchi, and lungs are frequently involved in infants. When the larynx or trachea is inflamed, there is usually present a very troublesome cough, and at times great dyspnea and cyanosis. Breathing and feeding are greatly interfered with, and death due to asphyxia has been known to take place. Bronchitis in the course of influenza is an unfavorable complication in infants, because it is very often followed by pneumonia, which frequently has a fatal outcome. At times the diagnosis of pneumonia in infants causes great difficulty. No signs in the lungs can be elicited either on percussion or auscultation, and pneumonia is not suspected until revealed at autopsy. The presence of dyspnea, in combination with the moving of the alæ nasi with respiration, and an extreme pallor should make one suspicious of pneumonia whether or not physical signs of consolidation are present in the lungs. Very frequently when pneumonia is present, serous meningitis or meningismus is often seen in infants.

Diagnosis.—During an epidemic there is usually no great difficulty in making a diagnosis of influenza. There is, likewise, little difficulty in sporadic cases, if the typical symptoms of the disease are present. In doubtful cases, an examination of the bronchial secretions will at times show the presence in great numbers of the influenza bacilli. But as this method of examination is very difficult, it is almost impossible to make use of it except in hospitals with good laboratory facilities. At times the diagnosis is so difficult, that it can be made only by exclusion. At other times an absolute diagnosis is impossible. It should be remembered that other organisms can cause the same symptoms as the influenza bacillus. A differential diagnosis from a bacteriological point of view is not very important, since there is no specific for influenza, and treatment in all of these cases is the same. According to Rotch, profound prostration, out of all proportion to the intensity of the disease, is of great diagnostic value.

Differential Diagnosis.—The diseases with which influenza is at times confused are (1) typhoid fever, (2) cerebrospinal meningitis, (3) malaria, (4) septicemia, (5) measles, (6) scarlet fever, (7) tuberculosis.

In **typhoid fever** the onset is usually not so sudden as in influenza, and the temperature curve is more regular. There is usually a low white-blood count in typhoid fever, while in influenza the white-blood count may be normal or higher than normal. During the second week of the fever the absence of rose-spots, a negative Widal reaction, and the absence of typhoid bacilli from the blood rule out typhoid fever. At times, however, typhoid fever in children runs a very atypical course; consequently a differential diagnosis is extremely difficult to make.

Cerebrospinal Meningitis.—At times the sudden onset of influenza with fever, headache, great restlessness, pain, vomiting, delirium, and muscular rigidity may very closely simulate cerebrospinal meningitis. Opisthotonos, which is frequently caused by an enlargement of the cervical glands, may be present. This group of symptoms is not infrequently seen in infants with a spasmophilic diathesis. Lumbar puncture with a chemical and bacteriological examination of the spinal fluid will make the diagnosis clear.

Malaria.—The intermittent temperature with an enlarged spleen, and at times chills, may cause confusion with malaria. The absence of the plasmodia from the blood, however, and the course of the disease rule out malaria.

Septicemia.—At times influenza characterized by remittent and intermittent temperature, accompanied by chilly sensations or real chills may simulate septicemia. This class of cases must be observed for some time before an accurate diagnosis can be made. A blood culture is at times of value.

Measles.—The catarrhal symptoms observed in influenza, accompanied by sneezing, coughing and a macular rash, which is sometimes present, may closely resemble measles. The presence of Koplik spots in measles is diagnostic.

Scarlet Fever.—An erythematous eruption is sometimes present in influenza which may be confused with scarlet fever. The eruption in influenza, as a rule, however, lasts only a few hours, and its early disappearance will rule out scarlet fever. In influenza one rarely finds the so-called "strawberry" tongue which is characteristic of scarlet fever.

Tuberculosis.—A negative tuberculin reaction, and in very suspicious cases a negative Roentgen-ray examination of the chest, will differentiate influenza from tuberculosis, but often a definite diagnosis cannot be made for some time.

Complications and Sequelæ.—The complications and sequelæ in influenza are very protean in character. Almost any tissue or organ of the body may become affected, either by the influenza bacillus itself, or by some of the numerous secondary invaders.

Skin.—Besides the skin lesions such as urticaria, erythema, and herpes, which have already been mentioned under the symptoms of influenza, there may be at times, especially in infants, a rather severe furunculosis following on an attack of influenza. Erysipelas of the face, hands, arms, legs, and other parts of the body has been observed.

Glands.—The cervical glands often become enlarged, and remain so for many weeks or months after the initial attack. At times suppuration takes place. Occasionally an enlargement of various groups of lymphatic glands occurs, accompanied by fever, which may last for several days or weeks. At times, after or during an attack of influenza, Pfeiffer's so-called "Glandular Fever" is observed. This condition is unquestionably always preceded by an inflammation of the nasopharynx. Retropharyngeal abscesses are not uncommon in infants, and are usually secondary to influenza.

Joints and Bones.—Arthritis is rare. Periostitis and osteomyelitis may occur, and are often very severe in character. Cases of osteomyelitis have been observed in which the infection has been so profound that death has resulted in the course of a few days.

Ears.—Purulent otitis media and mastoiditis are very frequently observed. Involvement of the mastoid would be less common if paracentesis of the drum membrane were delayed until bulging was actually present. There is no question that many cases of mastoid disease have resulted from needless incision of the membrane.

Eyes.—Conjunctivitis is common. Corneal ulcerations, iritis, and iridocyclitis, as well as other eye complications, are rarely seen in children and infants.

Peritonitis is at times observed, especially in young children and infants.

Circulatory System.—Influenza affects the heart in various ways. Functional cardiac disturbances are not at all uncommon, and may cause weakness, prostration, and debility for very long periods of time. Irregularity of the heart's action is frequently observed. Bradycardia occurs more often in influenza than in any other infectious disease. Tachycardia is less frequent. The toxins of influenza may attack the heart muscle or its valves, causing myocarditis and acute endocarditis. Subacute infective endocarditis with bacteriemia has been described (Brill). Pericarditis usually occurs secondary to pneumonia or pleurisy. Severe anemia at times follows influenza.

Respiratory System.—Bronchitis has been mentioned under the symptoms of influenza. Pneumonia is the most important complication, and is often the decisive factor in influencing the mortality of the disease. The bronchial type of pneumonia is by far the most common in children, and may be due to the influenza bacillus itself, or to some other organism. The lobar type of pneumonia is occasionally seen. Empyema is a dreaded complication, especially in infants. Tuberculosis at times follows influenza, or influenza may make a latent case of tuberculosis active. Extensive subcutaneous emphysema occasionally occurs in the more severe forms of pneumonia.

Genito-urinary System.—Albuminuria with hyalin and granular casts is met with frequently in influenza when the temperature is high. This condition usually lasts only for a few days. Real nephritis occurs in a small number of cases. Hemorrhagic nephritis is occasionally met with, and at times is very severe in character. Cystitis and pyelo-cystitis are not infrequently seen in infants and young children. They are usually due to the colon bacillus.

Nervous System.—Many diseases of the nervous system are attributed to influenza. Cases of meningitis occur in which the influenza bacillus has been isolated from the spinal fluid. Encephalitis and myelitis occasionally are seen. Neuritis, which is very rare in children, is observed at times.

Convalescence.—Children may complain for many weeks and months of great depression, weakness and fatigue, and convalescence may be greatly prolonged. Infants may suffer from malnutrition for months after an attack of influenza.

Prognosis.—The prognosis of influenza in children should always be a guarded one. One cannot tell at the beginning of the disease whether the bronchi and lungs will become affected, or whether a severe otitis media or a purulent meningitis will develop. Prognosis is usually favorable unless the lungs or heart are involved. According to various observers, the mortality in older children is less than 2 per cent. Death is caused not by the influenza itself, but by its many complications. In infants, especially where there are nutritional disturbances, the mortality is very high. Infants with a spasmophilic or exudative diathesis are usually severely affected by influenza. Nearly as many infants die in institutions from influenza as from "summer diarrhea."

Prophylaxis.—Because influenza is generally considered a very mild disease, prophylactic measures are to a great extent neglected. We would pay more attention to the prevention of this disease if we realized that severe complications very often occur during its course, and that in consequence of these complications the death-rate in infants and young children is very high.

Injections of vaccines prepared from the influenza bacillus have been used extensively during the recent epidemic of 1918–1919. The consensus of opinion seems to be that prophylactic vaccination against influenza is still in the experimental stage. Favorable results have not been observed by the author in a rather large number of cases. Vaccines from stock cultures of one or more organisms were reported by the American Public Health Association to be of no value.

During epidemics children should be removed from school and kept away from public places such as street cars, theaters, and the like. Affected members of the household, as in other acute contagious diseases, should be rigidly isolated. When this is not feasible, as in the case of mothers who are nursing their infants, the mothers should only come in contact with the infants during nursing time, and then they should wear gauze masks over the nose and mouth. The discharges from the nose, throat, and the excreta should be disinfected or destroyed. Nursery maids suffering from influenza should not come in contact with the children under their care until they have completely recovered from the disease. In this way we can lessen the morbidity of the disease to a great extent, which in some epidemics has affected 50 per cent. of the population.

Treatment.—There is no known specific for influenza. The employment of vaccines and serums has not been productive of favorable results. We can lessen the symptoms of the disease and make the patient more comfortable, and, to a certain extent, prevent complications and hasten recovery.

General Treatment.—The patient should be kept in bed until several days after the temperature has dropped to normal and the acute symptoms have disappeared. The temperature of the room should be about 68°F. Although in recent years much has been written about the beneficial effects of cold air as a therapeutic measure, there is no question that moderately fresh air is much more soothing to influenza patients than cold air. A hot-water bag should be placed at the patient's feet. In the beginning of the disease hot drinks, such as lemonade, milk, or weak tea with milk, should be given. If the bowels have not moved freely a mild saline laxative should be ordered. As a rule children do not mind taking citrate of magnesia, of which four to six ounces should be given. Too severe cartharsis is very weakening and is to be avoided. If the bowels have moved well at the beginning of the disease, a laxative need not be given. If the bowels have a tendency to be costive, daily enemata of normal saline solution or of soap suds are often of value. Liquid petrolatum in one-half to one ounce doses, given at night, is also useful in regulating the bowels. The diet should at first consist of fluids—plenty of water, milk diluted with cereal water, soup and gruels. Later on eggs, cereal, ice-cream, and the like are permitted. Warm tub baths or tepid sponge baths, frequently repeated, tend to make the patient more comfortable and to reduce the temperature.

For the severe *muscular pains, headache, and irritability* which are frequently present in influenza, some one of the numerous coal tar products is indicated. Their choice depends upon individual preference. All coal tar products, however should be used with great caution in influenza on account of their depressant action. Phenacetin, sodium salicylate, or antipyrin, given in small doses at one, two, or three hour intervals afford much relief. These drugs make the patient more comfortable, but do not influence the course of the disease. When prostration is present, it is at times advisable, unless there is much irritability, to give in addition a grain or two of caffeine sodium benzoate or caffeine sodium salicylate every three hours. If the restlessness is very great, sodium bromide in 5 or 10 gr. doses by mouth a few times a day, or chloral hydrate in 5 gr. doses by rectum are valuable. Some digitalis preparation should be used early in the more severe forms of influenza.

Nose and Throat.—Local treatment of the nose and throat is indicated in almost every case of influenza. Early in the course of the disease the application of a 2 per cent. solution of silver nitrate to the nose and throat once or twice daily has proved very efficacious. Instead of the silver nitrate, a 10 to 15 per cent. solution of argyrol may be used. In infants the coryza is at times very troublesome. The nares are occluded, and breathing and nursing are much interfered with. In consequence pneumonia and inanition often result. In these cases instillation into the nose of a few drops of liquid petrolatum or of normal saline solution very gently with a medicine dropper gives much relief. In the more severe cases, adrenalin inhalant solution diluted with four parts of sweet almond oil or adrenalin chloride solution 1:1000 diluted with four parts of normal saline solution used in the same way are of great value. Irrigation of the nose is not recommended on account of the danger of consequent middle ear infection. Spraying the throat at frequent intervals with a mild alkaline antiseptic solution, such as liquor alkaline antisepticus, is indicated unless the patient rebels too much. Cold, moist compresses applied around the neck and frequently changed are very soothing.

The Middle Ear.—In children and even in very young infants, one can tell with a great deal of accuracy, by means of the electric auriscope, whether or not the middle ear is involved. Inasmuch as otitis media frequently occurs in the course of or following influenza, and its early recognition is of great importance, the ears should be frequently examined. In older children pain is usually a prominent symptom when the ears are involved, but in infants not infrequently the first sign of this condition is a purulent discharge from the ears. When an examination of the ears has shown that congestion is present, a few drops of a 10 per cent. solution of carbolic acid in glycerin, warmed and dropped into the ear every few hours, affords much relief, and has also a curative action. If bulging of the membrane is present, a paracentesis should be performed at once, after which the ear should be irrigated with a warm normal saline or boric acid solution every two or three hours until the discharge returns clear.

Skin.—For the urticaria which is at times present, the following solution rubbed into the skin at frequent intervals gives relief:

Calamine	5.0
Zinc oxide	5.0
Lime water	50.0
Rose water	50.0

Glands.—The cervical glands are frequently enlarged after an attack of influenza and may remain so for many weeks or months. Local treatment of the nose and throat often has a favorable influence. In the very obstinate cases, removal of adenoid tissue alone, or in combination with the enucleation of the tonsils, will at times cause a disappearance of the glands. Administration of iron or arsenic is often of value. In some cases the glands persist in spite of all treatment and make one strongly suspect tuberculosis.

Cough.—If the cough is mild, steam inhalations of one teaspoonful of compound tincture of benzoin to 1 qt. of water often gives relief. For the more severe cough, sodium bromide or codein is indicated.

Bronchitis.—For the complicating bronchitis, from 8 to 10 drops of liquor ammonii anisati, well diluted with water and given at frequent intervals, is of value. Expectorant cough mixtures should not be used. They rarely relieve the cough in infants and young children, and may do harm by causing gastric disturbances.

Pneumonia.—It should be remembered that the pneumonias complicating influenza are usually of the bronchial type, and very often are of serious consequence. Stimulation should therefore be given early. Following Jacobi's teachings it seems advisable to give rather large doses of a reliable digitalis preparation three or four times daily until the acute stage of the disease has passed. In addition to the digitalis, camphor and caffein should be given alternately every two or three hours. Frequent sponge baths, the temperature of which should be regulated according to the patient's temperature, are of great benefit. If a troublesome cough is present, codein is indicated. The use of vaccins and of convalescent blood and serum has been of little value in pneumonia. When resolution is much delayed, fresh air and sunlight with good nutritious food is of great value.

In influenza with *meningeal symptoms* lumbar puncture performed early and repeated after 12 to 24 hours, if necessary, is almost invariably of much benefit. Chloral hydrate in doses of from 5 to 7 gr. given by rectum in an ounce or two of water, and repeated in one-half to one hour when indicated, is also of great value in this class of cases. Sodium bromide aids much in quieting the patient and must often be given for many days.

Convalescence.—The patient is often left in a very weakened condition after an attack of influenza. Anorexia, sleeplessness, depression and fatigue may be present for many weeks or months following the attack. At times a slight rise in temperature due to weakness persists for some time. The best tonics in convalescence are fresh air, sunlight and good nutritious food. A change of climate and different surroundings will often be of great benefit. Arsenic trioxid and strychnin are of value. The syrup of ferrous iodides is indicated when anemia is present.

CHAPTER CXLIX

TETANUS

(Lock-jaw)

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Definition.—Tetanus is an acute, subacute or chronic intoxication of the nervous system caused by infection with the tetanus bacillus. The disease is usually endemic, although epidemic outbreaks have occurred in times of war and are traceable to some definite source; the disease occasionally becomes epidemic in the tetanus of the new born, or following the use of infected small-pox vaccin, and following surgical operations from infected catgut ligatures, etc. So-called idiopathic tetanus is probably consequent upon some mild injury to which the patient has given little attention.

Historical.—The disease was known to the ancients and descriptions of it can be found in the writings of Hippocrates, Galen, Celsus and Areteus. Even in early times tetanus was recognized as a disease which affects the nervous system principally, but the infectious nature of tetanus was not understood until 1880, when Sternberg[1] announced that he could produce the disease by the injection into animals of garden earth. The specific organism causing the disease was discovered in 1884 by Nicolaier,[2] who found a long, slender bacillus in the wounds of patients suffering from tetanus. The isolation of the bacillus in pure culture was accomplished in 1889 by Kitasato,[3] who made use of the marked resistance of the tetanus spores to heating in obtaining his pure cultures. Baumer, Marie and Gumprecht[4] were among the first to show that the toxins of tetanus were carried to the cord through the nerves and not through the blood and general lymph channels.

Bacteriology.—The tetanus bacillus is widely distributed and is to be found as a common inhabitant of the soil. It is especially abundant in soil which has been fertilized by manure. In young cultures the bacillus appears as a long, slender rod, which is actively motile. The bacilli vary from 2 to 4μ in length and from 0.3 to 0.5μ in thickness. In older cultures the so-called "drum-stick" shapes are due to the presence of a single round spore at one pole of the organism. The width of this spore is greater than any other section of the cell. The bacillus takes a Gram-positive stain and the spore is easily demonstrated with either Gram or methylene blue stain, or by the special double stain described by Ziehl. The bacillus is strictly anaërobic; it liquefies gelatin, and in stab cultures with this medium gives the appearance of an arborescent growth.

Tetanus can be produced in guinea pigs, rabbits and other animals by the inoculation of a pure culture of the bacillus. A very active toxin develops in anaërobic bouillon cultures, which in minute amounts gives rise to tetanus in the lower animals. Brieger[5] has isolated two active principles from tetanus toxin; one he called tetano-spasmin and the other tetano-lysin. Both are of alkaloidal composition and are virulent poisons. The former produces spasm of voluntary muscles, the latter has a lytic action on red-blood cells. The local action of the tetanus bacillus is aided when there is a simultaneous infection with one of the pyogenic organisms, especially if the tissues have been bruised and lacerated at the same time. According to Meyer and Ransom,[6] and Marie and Morax,[7] the toxin produced locally at the site of infection passes to the nerve centers in the spinal cord by way of the axis cylinders of the motor neurons. According to more recent investigations the toxin passes to the central nervous system by way of the perineural lymphatics.

Trauma is by far the most important predisposing etiological factor. During the recent war this fact was recognized and every wounded soldier received at the first possible opportunity a prophylactic injection of tetanus antitoxin. Fourth of July wounds have always been an important element in the causation of tetanus although with the inauguration of a sane and safe fourth of July celebration tetanus from this source has become less frequent. Tetanus occurs especially during the summer months of the year. It is found more frequently in males than females on account of the greater exposure of males to trauma.

Pathology.—Few definite lesions are found at post-mortem. The gray matter shows occasionally hyperemic, cellular exudate in the perivascular spaces and chromatolysis of the cells in the neighborhood of the anterior horn. Smaller and larger hemorrhages have also been noted.

Symptoms.—The period of incubation in man varies from two days to two weeks, the normal period being from seven to nine days. In the subacute and chronic form tetanus may not develop until months after the injury.

The onset of tetanus may be preceded by mild prodromal symptoms, of which headache and pain in the back are most frequently noted. The symptoms may begin suddenly or insidiously. In many of the typical cases the first symptoms are those of slight stiffness of the muscles of the neck and lower jaw, so that the mouth can only be opened with difficulty. Spasm of the masseter muscles supervenes. The facial muscles appear immovable, the teeth are clenched and the jaw is locked. The corners of the mouth are drawn down, and efforts of the patient to open the mouth results in wrinkling of the forehead and a protrusion of the lips, which give the appearance of the so-called sardonic grin, or risus sardonicus (Fig. 27).

Involvement of the muscles of deglutition gives rise to difficulty in swallowing. The muscles of the trunk and limbs become rigid, a condition known as *orthotonos*. Involvement of the muscles of the back results in a marked curvature of the spine, producing a condition known as *opisthotonos*. Rigidity and contraction of the anterior abdominal muscles may bend the body forward and produce the condition known as *emprosthotonos*. A lateral curvature, resulting from unilateral spasm of the muscles of the spine, is called *pleurothotonos*. Ultimately all voluntary muscles may be involved. The arms may be bent or extended, the legs are extended and the body curved. This is the typical tetanic condition and is often preceded by clonic convulsions of a most painful character. Dyspnea and cyanosis, due to paroxysm of the glottis and involvement of the respiratory muscles, occur. During such a paroxysm the breathing is difficult and sterterous, and the patient often foams at the mouth. Slight external irritation, such as a touch, a jar, a sudden sound, a flash of light or a draught, is sufficient to initiate a convulsive seizure. The spasms may last from a few seconds to one or more minutes. There may be only a few during the day, but at times they are almost continuous, the

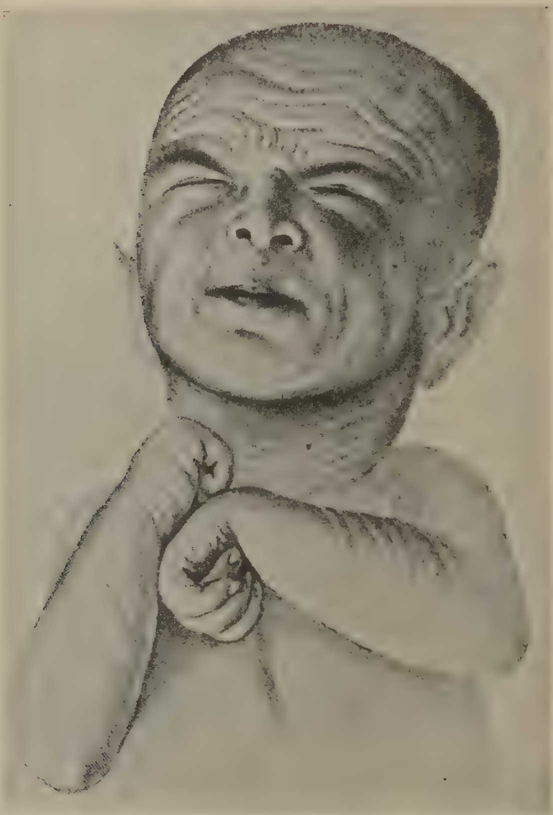

Fig. 27.—Tetanus neonatorum in a 16 day old infant. (After Knopfelmacher.)

body remaining in a more or less constant rigid state. All the reflexes are markedly exaggerated, and the sensorium remains clear.

Profuse sweating is generally noted. The temperature rises a few degrees, generally showing a very high degree in the preagonal stage. Spasm of the sphincter muscles makes urination and defecation difficult. Death occurs from profound exhaustion and inanition, or arrest of the heart's action from spasm or paralysis leading to cardiac dilatation. Death may also result from respiratory failure due to laryngeal spasm or spasm of the diaphragm. In the very acute cases death occurs within two or three days. Recovery is possible, however, even in the more aggravated cases. This is indicated by a gradual relaxation of the rigidity and greater infrequency of the spasms.

The cephalic form of tetanus, which has been described by Rose,[8] is a variety following wounds in the distribution of the cranial nerves. The spasms are confined to the muscles of the jaw, the pharynx and esophagus, and there is an associated paralysis of the side of the face on which the injury has taken place.

Milder cases of tetanus may have as the only symptom a slight rigidity of the masseter muscles. The difficulty in deglutition may in some cases suggest the diagnosis of hydrophobia.

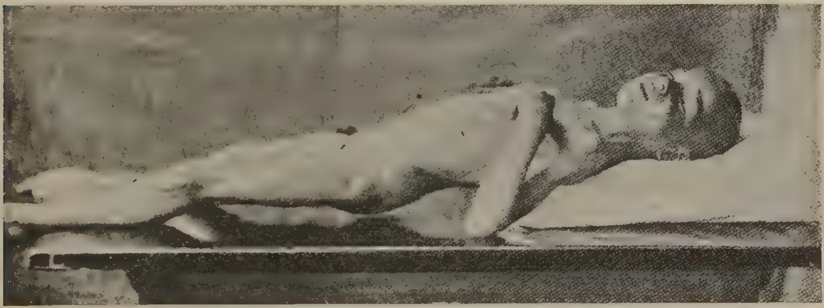

FIG. 28.—Tetanus neonatorum. (After Stenitzer.)

Tetanus Neonatorum (Fig. 28).—Tetanus of the newborn occurs as a result of infection at the time of ligation of the cord or during the separation of the stump. The onset is from the fifth to the twelfth day after birth. The most characteristic symptom is trismus. The lower jaw is fixed making nursing difficult or impossible. The muscles of deglutition are affected, swallowing is impossible and the fluids introduced are rejected. The spasms extend to the trunk or limbs, with a progressive stiffening of the entire body. The arms and legs are extended, the back arched. In some cases the arms may be flexed, and the hands tightly clenched, with the legs half flexed at the hip and knee joints. During the intervals the spasm relaxes and the child may obtain some nourishment. In a fatal case the spasms become almost continuous, the whole body remaining rigid.

Von Reuss quotes the following significant statistics on tetanus neonatorum. According to Miron[9] (for the year 1904), of 23,398 children who died in Roumania within the first month, 10,257, or nearly half, died from tetanus. He corroborated the diagnosis in 19 of these cases by finding the tetanus bacillus in the umbilical stump and in the material obtained from the clay floors of the houses in which these cases occurred. According to Paulin[10] (1906), in Denmark 50 to 60 children die yearly from tetanus. It has been reported that in Cayenne 10 to 25 per cent. of the newborn succumb to tetanus (Flesch).[11] Also among the black population in South America tetanus neonatorum is supposed to be very widespread (Anders and Morgan).[12]

This form of tetanus is especially common in the Hebrides, Cuba and Jamaica. Among the colored population of Louisiana, Maryland, Michigan and the District of Columbia the disease was prevalent at one time.

The mortality from tetanus neonatorum is very high, fully 90 to 95 per cent. of the cases terminating fatally. The majority of the cases reported have died, after a short incubation period, between the sixth and tenth days. The duration of the disease in the fatal cases may be no more than one to two days, but in those terminating favorably the symptoms may persist for two to three weeks.

For determining the prognosis Flesch gives the following points:

1. Length of incubation period (generally difficult to estimate).
2. The time of antitoxin administration.
3. Degree and extent of rigidity.
4. Possibility of taking food.
5. State of body temperature.

The following case, quoted by von Reuss[13] from the case records of the Vienna Children's Hospital, will illustrate that even severe cases have recovered.

A. B. Tetanus neonatorum, refusal of food and trismus on the eighth day. On being lifted on the twelfth day severe general tonic spasms. On fifth and sixth days of disease, injections with 30 c.c. tetanus serum. In spite of these injections an increase of symptoms continued. High intermittent fever (107°F.). Almost impossible to give food with a catheter so that the child nearly starved for 14 days. Fluid given subcutaneously and by enemata. The weight of the body sunk from 7¾ lb. to 6 lb. The symptoms only began to diminish in intensity on the twenty-first day, when the child, almost reduced to a skeleton, began to take the breast. Improvement then progressed rapidly. In the ensuing months the child progressed normally.

The treatment recommended by von Reuss consists of the injection of 250 units of tetanus antitoxin by lumbar puncture and subcutaneously, to be repeated the following day. Of special importance, he says, is the symptomatic treatment, which is directed toward the mitigation of the spasms, which are accompanied by a great waste of tissue. The most suitable remedy is chloral hydrate, which is administered by enema in a 1 per cent. solution, in single doses of about 0.5 gm. three to four times daily. The chloral may be administered daily for some time, which is not possible with other narcotics, as, *e.g.*, with the momentarily effectual inhalations of chloroform. The administration of sedatives per os (bromides, calcium or chloral) meets with difficulties the same as feeding. Great care must be used with the latter. Only in mild cases will the child take the breast or the bottle, and as a rule feeding with a spoon is very unsatisfactory. In such cases food must be given with a catheter passed through the nose. Tube feeding sometimes meets with obstruction and owing to vomiting does not fulfill its purpose. The effort must then be made to assure, to some extent, the necessary fluid by subcutaneous infusions and injections into the bowel. Nutrient enemata with mother's milk may also be tried.

Chronic Cases.—In these cases the onset is more protracted, and the symptoms less pronounced. The trismus is less marked, nourishment is possible. The symptoms may become temporarily aggravated. In favorable cases the intervals between the spasms grow greater until the stage of convalescence is reached. There are often recurrences of the disease, especially if tetanus antitoxin has not been used. Muscular contractures or rigidity may persist, especially of the muscles of the jaw.

The abnormal forms of tetanus have been classified by Courtois-Suffit and Giroux[14] in an interesting study published after an extensive experience with tetanus during the recent war. They divide these forms into:

(**a**) **Splanchnic Tetanus.**—Following abdominal operations. Always fatal. Characterized by non-generalization of the contractures, but with involvement of the muscles of deglutition and respiration.

(**b**) **Cephalic Tetanus.**—(1) Non-paralytic type. Three forms:

(*a*) Simple form shows trismus with contracture of certain face muscles.

(*b*) Dysphagic form with involvement of pharyngeal muscles.

(*c*) Hydrophobic form, characterized by violent convulsive spasms involving muscles of face, neck, pharynx and diaphragm.

2. Paralytic type. Rare. Facial paralysis with contracture of certain face muscles.

3. With paralysis of motor nerves of the eye. Follows trauma of eye and adjacent parts. Third nerve always involved, fourth and sixth nerves may also be paralyzed.

4. With paralysis of hypoglossal. Rare. Syndrome of labio-glosso-laryngeal paralysis.

(c) Unilateral Tetanus.—Symptoms predominate on one side of the body, even during generalization of convulsions, giving rise to pleurothotonos.

(d) Tetanus of the Limbs.—(1) Monoplegic form. Stiffness of one limb with slight transitory trismus.

2. Paraplegic form. According to seat of contractures these are distinguished as:

(*a*) A superior paraplegic form—upper arm, forearm, and hands are forcibly flexed.

(*b*) Inferior paraplegic form—lower limbs in forced extension.

(e) **Localized Tetanus.**—Abdominal-thoracic type. Very rare.

(f) **Attenuated or Chronic Tetanus.**—Developing slowly after a prolonged incubation. Rare. Symptoms of slight stiffness of the muscles of the wounded limb and of the masseter muscles develop slowly. Show muscular hypertension and exaggerated reflexes.

Diagnosis.—The typical cases with an acute onset are fairly characteristic and the diagnosis is not difficult. Certain affections, however, bear a clinical resemblance to tetanus and must be distinguished. Among these are strychnin poisoning, tetany, hydrophobia, cerebrospinal meningitis and encephalitis lethargica.

In strychnin poisoning there is a history of ingestion of the drug, followed immediately by symptoms. These are violent convulsions from the commencement, with intervals of complete relaxation. Trismus is not an early symptom. There is rapid termination in death or recovery. Chemical examination of the gastric contents shows the presence of strychnin.

In tetany the symptoms are not as severe as in tetanus. They may be limited to the extremities and the laryngeal muscles. There is also an increased mechanical excitability of the motor nerves and a characteristic posture. The age is important, tetany occurring especially in young individuals.

In hydrophobia there is a history of the bite of an animal. The reflex spasms of the respiratory muscles are especially marked. Trismus and general bodily spasms are absent.

In cerebrospinal meningitis there is rigidity of the cervical muscles. Trismus is absent. Other clinical phenomena, such as vomiting, herpes, disturbance of the sensorium, will help in the diagnosis.

The myoclonic form of encephalitis lethargica may resemble closely the various types of localized tetanus. The frequency of diplopia, of somnolence and the presence of positive spinal fluid findings will help in the diagnosis of encephalitis lethargica.

Prognosis.—This varies with the nature of the wound. Severe trauma associated with a short period of incubation gives the highest mortality. Cases appearing late after an injury give a much better prognosis. The severity and progress of the symptoms are also a very good guide in the prognosis. When the spasms remain confined to the jaw muscles the prognosis is good. The prognosis is rendered more favorable if the patient receives an early intraspinous injection of antitoxin. The prognosis in cases not treated with tetanus antitoxin is not as good as when early and prompt serum treatment has been instituted. In the Medical and Surgical "History of the War of the Rebellion," Part 3, Surgical History, p. 818, the following summary appears:

Of 246,712 injuries by weapons of war 505 (0.2 per cent.) or a little over 2 in 1000, were followed by tetanus, which is regarded as not a large proportion. The seat of the injury and the results are tabulated as follows:

Seat of injury	Total cases	Recoveries	Deaths	Ratio of mortality
Head, face, neck	20	1	20	95.2
Trunk	55	5	50	90.9
Upper extremity	137	18	119	86.8
Lower extremity	292	30	252	89.7
Aggregate	504	54	441	87.5

The recoveries were chiefly in the slighter or more chronic cases; and the later the occurrence of the disease after the injury the greater the chance of life. The duration of the disease in 358 cases did not exceed three days in 203 cases, and of these only two recovered. The ongest duration among the fatal cases was 27 days.

The effect of the prophylactic administration of tetanus antitoxin on the prognosis of tetanus is brought out in an interesting way by the following tables given by Bruce[15] in the final analysis of cases of tetanus treated in home and military hospitals during the recent war.

Table 1

Number of cases	Inoculated	Recovered	Died	Mortality, per cent.
214	On day of wound	215	49	18
62	1 day after wound	48	14	22
14	2 days after wound	12	2	14
5	3 days after wound	4	1	20
7	4 days after wound	5	2	30
8	More than 4 days after wound	8	0	0

Table 1 gives the information in regard to the question what influence has promptitude in giving prophylactic injections on the rate of mortality. The table shows that cases developing tetanus after prophylactic injections run as a rule a mild course.

Table 2

Number of inoculations	Number of cases	Recovered	Died	Mortality, per cent.
Received 1	125	94	31	20
Received 2	127	103	24	19
Received 3	52	43	9	19
Received 4	38	35	3	8
Received 5	14	13	1	7
Received 6	2	2	0	0

Table 2 represents the rate of mortality of cases of tetanus which have received one to six prophylactic injections.

TABLE 3

Analyses	Number of cases	Recovered	Died	Mortality, per cent.
1914–1915	231	98	133	58
1915–1916	195	99	96	49
August to October, 1916	200	127	73	37
October to December, 1916	100	69	31	31
December, 1916 to March, 1917	100	81	19	19
March to June, 1917	100	71	29	29
June to September, 1917	100	85	15	15
September to December, 1917	100	84	16	16
December, 1917, to April, 1918	100	76	24	24
Total	1226	790	436	35.5

Table 3 shows in an interesting way the distribution of cases of tetanus from August, 1914, to April, 1918. It shows how the mortality rate from tetanus diminished as the war progressed. After 1916 the mortality rate was greatly diminished by the more thorough prophylactic use of repeated doses of tetanus antitoxin in the wounded.

TABLE 4

Number of inoculations	Sixth hundred		Seventh hundred		Eighth hundred		Ninth hundred	
	Number of cases	Average incubation period, days	Number of cases	Average incubation period, days	Number of cases	Average incubation period, days	Number of cases	Average incubation period, days
0	..	..	..	..	7	83	2	20
1	38	45	36	47	25	28	27	22
2	31	49	31	66	33	30	31	23
3	10	39	15	62	13	62	14	56
4	2	127	5	60	16	70	15	111
5	2	97	2	79	3	94	6	134
6	1	68	1	122				

Table 4 gives the results of one or more inoculations of tetanus antitoxin on the period of incubation. It shows how this period is markedly prolonged in those cases that have received multiple prophylactic injections.

Prophylaxis consists of two parts:

1. The thorough cleansing of the wound.
2. Prophylactic injections of tetanus antitoxin.

The local treatment depends on the cause of the injury. Bullets and pieces of shrapnel should be removed. If the wounds are ragged and soiled, the tissues should be trimmed, enlarged if necessary, and thoroughly cleaned. Tincture of iodin or carbolic acid, followed by alcohol, may be used in smaller wounds. In fourth of July injuries, the cotton wadding of the blank cartridge is carefully searched for and removed. Extensive wounds with sinuses leading from them should be carefully treated. The recesses in such wounds are opened and a free supply of air admitted.

To prevent tetanus neonatorum the umbilical stump must be treated in a thoroughly aseptic manner and an antiseptic drying powder, such as aristol or boric acid powder, applied.

The great value of one or more prophylactic injections of tetanus antitoxin has been conclusively demonstrated in the World War. The following rules should be observed in regard to such preventive inoculations:

(*a*) Every wound received in war, and all wounds that have been contaminated with soil, all fourth of July wounds and penetrating wounds caused by rusty objects such as nails should be regarded as suspicious and requiring prophylactic injections of tetanus antitoxin.

(*b*) The injection of antitoxin should be given within 24 hours. This will prevent the tetanus toxin from forming and diffusing itself through the body.

(*c*) A single injection of tetanus antitoxin is often *not* sufficient. This is especially true in the case of contused wounds, when it becomes advisable to give two, three or even four injections at intervals of eight days.

(*d*) The prophylactic dose of tetanus antitoxin is 1000 units injected subcutaneously. A similar amount should be given when the injection is repeated at the end of 7 to 10 days.

(*e*) No danger is to be apprehended from a second subcutaneous injection of antitoxin, if the patient has tolerated well the first injection.

Treatment.—The treatment of an actual case of tetanus can be divided into (1) general and symptomatic treatment, which consists of careful nursing, antispasmodic treatment to relieve muscle spasm and special attention to nutrition to preserve bodily strength. (2) Specific treatment with tetanus antitoxin.

General and Symptomatic.—The patient is kept as quiet as possible in a darkened room far removed from noise. Mouth feeding should not be attempted in the acute cases. Rectal feeding is indicated under such conditions. An enema consisting of milk 1 pt. (500 c.c.) nutrose, 2 oz. (60 gm.) and one teaspoonful of salt is recommended by v. Leyden, and should be given twice daily. The amount should be in proportion to the age of the child. For children under five years not more than 2 to 4 oz. (60–120 c.c.) should be given; for children from 5 to 10 years, 8 oz. (240 c.c.), and for older children 12 oz. (360 c.c.). In the more subacute cases, if the trismus is not too marked, a liquid of high caloric value is advisable. A mixture is made of 1 qt. of milk (1000 c.c.), two eggs, 4 oz. (120 gm.) sugar, and ½ pt. cream (250 c.c.). This is divided into three meals. For children, the amount given should be in proportion to the age. If the trismus prevents the opening of the mouth, a rubber catheter can be passed through the nose or behind the rear molars and the liquid introduced into the stomach.

Antispasmodic Treatment.—One to two warm baths (temperature beginning with 97°F. and rising to 102°F.) a day, each bath lasting about 30 minutes, constitute a means of calming the patient.

In overcoming severe convulsions, chloroform may have to be used. The administration of sedatives is strongly indicated to keep the patient quiet, induce sleep and avoid the physical exhaustion as a result of the severe convulsions.

Sedatives such as *chloral* and *sodium bromide* are generally used. The dose of chloral varies with the age of the individual. From 5 to 20 gr. of chloral and from 10 to 40 gr. of sodium bromide may be given daily; chloretone may be used in doses of 10 to 20 gr. daily. *Morphine* is sometimes of great value in quieting the patient. It has the advantage in that it can be administered by hypodermic injection. In the newborn the dose is $\frac{1}{100}$ gr., in children of one year $\frac{1}{40}$ gr. and in those of five years $\frac{1}{12}$ gr. In older children the dose may be increased to $\frac{1}{10}$ or even $\frac{1}{8}$ gr. *Luminal* has been recently recommended by Stone as an excellent seative and hypnotic. The dose is from $\frac{1}{4}$ to $\frac{3}{4}$ gr., repeated twice daily.

The use of magnesium sulphate as a nerve sedative has been recommended by S. J. Meltzer.[16] The drug is dangerous because of its paralyzing effect on the respiratory center and should only be used by one who is acquainted with its dangers. When used, however, rationally and with the patient under constant observation it is relatively safe. The injections may be given intraspinously, intravenously or subcutaneously. For the intraspinous and intravenous injections the dose recommended is 1 c.c. of a 25 per cent. solution for each 20 lb. of body-weight. For subcutaneous injection the dose is greater. This method of injection is much safer, but it will not bring about relaxation in severe spasms. Magnesium sulphate may be used as an antispasmodic adjuvant to tetanus antitoxin, but it should not replace the use of the more important specific therapeutic agent.

Local Treatment of Wound.—Sinuses leading from the wound and pockets of pus should be freely opened up so as to allow a plentiful access of oxygen. Ordinary surgical methods are otherwise indicated. It is not advisable to amputate infected limbs, unless an urgent surgical indication is present. The mortality after such amputations is very high.

Local injections in the neighborhood of the wound of a 5 per cent. solution of carbolic acid are recommended by French and Italian authorities. This method has not been practiced to any extent in the United States and it is doubtful if it has any intrinsic value.

Antitoxin Treatment.—The intraspinous injection of tetanus antitoxin combined with an intravenous injection is considered as the most valuable means of neutralizing tetanus toxin.

Chloroform anesthesia may have to be resorted to so as to overcome the convulsions and relax the patient. A lumbar puncture is made and a somewhat larger amount of spinal fluid is removed than the amount of antitoxin to be introduced. If too viscid and flowing with difficulty the antitoxin is previously diluted with one to two volumes of sterile salt solution and introduced by gravity. The dilution of the antitoxin insures its more rapid dissemination throughout the spinal meninges.

The following procedure has been recommended by Park[17] and other authorities:

1. Inject intraspinally from 3000 to 10,000 units of antitoxin and repeat daily for three to five days. In cases of tetanus neonatorum the dose should be from 250 to 500 units.

2. Inject with first dose 5000 to 10,000 units intravenously to neutralize the tetanus toxin circulating in the blood. All the antitoxin given intraspinously passes to the blood within 24 hours and accumulates there.

3. Inject 10,000 units five days after the first lumbar puncture in case it is not repeated more than three times. This will maintain the antitoxic substances within the blood for several days to combat any toxins arising from sloughing tissues.

The important point to remember in connection with antitoxin treatment is to commence the treatment *as early as possible* and to give sufficiently large doses of serum. Even the delay of one-half an hour is of importance.

When time permits it is advisable to desensitize the patient in the milder cases by the method of Besredka before giving the injections. This is especially important in cases where previous prophylactic injections have been administered. The method consists of injecting a few drops of the antitoxic serum at intervals of 15 to 30 minutes until three or four injections have been given.

The Royal Army Medical Corps of Great Britain published in 1915 a pamphlet entitled "Memorandum of the Treatment of Injuries in War Based on Experience in the Present Campaign" in which some of the results of serum treatment in the recent war were well summarized. The following quotation is from the pamphlet.

"*Tetanus Antitoxin.*—This is the only treatment as to the employment of which there has been anything like general agreement. It has been used in one form or another in almost every case, and when cure has resulted it has commonly been given the credit. Whatever method be employed it is clear that three general principles must be covered to obtain the best results:

"1. It must be employed at the earliest moment possible; a dose of 1000 to 1500 units given at a time when there is little more than a fear that tetanus may develop may influence the course of the disease favorably.

"2. It must be given in large doses and these should be repeated until symptoms show signs of amelioration.

"3. It must be kept up, although in smaller and less frequent doses, well into convalescence, in order to obviate the tendency to relapse.

The most favorable results appear to have been obtained by the employment, in the first instance, of the intraspinal combined with the intravenous methods, the subcutaneous method being used to reinforce the others in the succeeding days or to replace them as the symptoms diminish in intensity.

"*Dosage.*—An initial intraspinous dose of 3000 units followed by the intravenous injection of doses ranging between 5000 and 20,000 units, according to the severity of the symptoms, has been reported in many instances to have had a favorable effect. In severe instances the intraspinous dose of 3000 units may be repeated the next day. The subsequent indications as to dosage depend upon the progress of the case; if this is favorable the above methods may be supplemented or replaced by the subcutaneous one, doses of from 5000 to 10,000 units being given every day or every second day.

"*Anaphylaxis.*—Symptoms of this grave condition are well known in animals to follow the administration of a second dose of the same serum, when the lapse of time between the two doses exceeds 10 to 12 days. There was more reason to fear its occurrence in men who had received a preventive dose of tetanus serum after being wounded, and who, on account of the development of the disease after an interval of 12 days or more, were given therapeutic doses of the same serum. Again, a large number of men who have returned to the front after recovery from a wound are again wounded, and the question has been raised as to the possible danger of giving another preventive dose of serum after an interval of some weeks or months. It is, however, well known that man is much less sensitive to anaphylaxis than the guinea pig and the rabbit, and this has been fully borne out by the experience of the war. In spite of close inquiries on the subject no certain instance of true anaphylaxis has been recorded. The few cases which have been mentioned in reports have, on investigation, turned out to be instances of serum sickness and to have had no grave results. It does not, therefore, appear to be justifiable to withhold the serum in the case of a man wounded for the second time; at all events it appears better to run the small and chiefly theoretical danger of anaphylaxis than the very grave one of tetanus.

"In cases in which there is reason to fear the occurrence of anaphylactic shock, various procedures have been recommended to lessen the danger. The majority of these are 'fractional' methods of administering the serum, a preliminary inoculation of two or three drops of the serum being given, in dilution, to be followed in five minutes by a dose of 0.5 c.c. If no outward symptoms result it is said that the dose may safely be inoculated 10 minutes later. A similar fractional method has been advised if the intrathecal methods are selected, but there has been no opportunity of judging of their value. Administration of the serum under chloroform anesthesia is also said to lessen the danger. If symptoms of shock develop in spite of these precautions, adrenalin has been stated to be useful, given intravenously in high dilution if the symptoms are urgent, hypodermically in a less urgent condition, in doses of a few minims of a 1:1000 solution."

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CHAPTER CL

HYDROPHOBIA

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Synonyms.—Lyssa (Greek); Rabies (Latin); La rage (French); Hundswut, Tollwut (German); rabbia (Italian); rabia (Spanish).

Definition.—Hydrophobia is an acute specific infectious disease occurring commonly in mammals. It is characterized (1) by a variably long incubation; (2) by an extremely short course and a practically certain mortality after symptoms develop; (3) by the localization of the virus chiefly in the central nervous system and the salivary glands, and (4) by the specific pathologic changes and symptoms resulting from this localization. It is communicated commonly by the bite of a rabid animal (most often a canine), less often by the introduction into a recent wound of the specific virus through contact with the saliva of an infected animal, or with other infected material.

Historical Note.—The disease has been recognized in writing since the time of Aristotle (about 300 B.C.) but the saliva of rabid animals was not shown to carry the virus until 1804, and it was not until Pasteur's studies (1884) that the entity of the disease was fully proven. Pasteur determined that the nerve tissue contents of the cerebrospinal canal contained the virus in a pure condition and that animals could be immunized against rabies by inoculations of an attenuated virus. Neither he nor others, however, were able to discover the morphologic cause of the disease.

Etiology.—**Geographical Distribution and Prevalence.**—Hydrophobia is reported as occurring in all parts of the world from the arctic regions to the tropics, except in a few areas such as Australia and several smaller islands that are free from it because of the rigid carrying out of the six month's quarantine law in regard to dogs. England, also, because of quarantine and periodic muzzling of dogs has been from time to time reported free. Recently several outbreaks have been reported supposed to be due to uninspected animals brought over in aeroplanes, or by other means.

Animals Affected.—All mammals, regardless of age, sex or season, may be infected. Certain birds are slightly susceptible. Those mammals most frequently exposed to the bites of rabid animals are most often affected. The dog is the most frequently infected (85 per cent.) probably because he is allowed to wander more at large. Wolves or other canines in special areas may stand next to the dog in frequency. Cattle stand next on the list (8 per cent.). Cats may contract the disease more often than is recorded, since they frequently develop the paralytic form which is not so readily diagnosed as the furious form. In general less than 1 per cent. each of other domestic animals (goats, sheep, horses, pigs) are affected. Humans seem to be the least of all attacked; and among human beings children are most frequently infected because of their greater liability to be attacked by mad dogs. It has been stated but not proved that rabbits, skunks and rats are natural carriers. In order to know in which cases prophylactic treatment should be given it is important to know about the disease in the biting animal. The number of susceptible animals bitten that come down with the disease is in proportion to the site and number of the bites. The nearer the bites are to the brain the more certain is the infection. In dogs, the average mortality is 40 per cent. Human beings now seldom show symptoms of rabies, owing to the widespread use of the preventive treatment, so the mortality percentage without treatment must be gathered largely from old statistics which are very incomplete. Babes gives the following table, compiled from statistics gathered early in his work in which the mortality in man is arranged in order of site and intensity of bites from different animals.

PERCENTAGE MORTALITY IN MAN

Character and site of bites	By wolf	By cat	By dog
Multiple and deep wounds about eye, nose or lips	100	70	60
Multiple and deep wounds about other parts of face	80	50	50
Multiple and deep wounds on other parts of uncovered body	40	40	20
Single and deep on finger or neck	20	20	15
Deep, on well-covered parts of body	15	10	3
Superficial, on uncovered parts of body	10	10	10
Same with hemorrhage	2	2	2
Contact with recent wounds in infected saliva	0.1	0.1	0.1
Contact of wounds more than 24 hours old	0	0	0

No authentic cases are on record of transference from man to man or from man to other animals. Glands from human beings are seldom infective for test animals. In New York City from 1900 to 1918 inclusive 139 deaths from rabies in human beings were reported.

Specific Living Agent.—Though it is known that the rabies virus is found free from other organisms in the central nervous system and in certain glands of the body, no one has yet been able to grow it freely outside of the body. Noguchi's work on the cultivation of the virus has not yet been corroborated. We know, however, some important characteristics of the virus. (1) It is filterable under special conditions of dilution and suction. (2) The virus is slightly resistant to certain agents and markedly resistant to others. This fact has a practical bearing in disinfection, in diagnosis and in certain methods of treatment. For example: Caterina and also Cumming have shown that formalin quickly kills the rabies virus in low dilutions. Hence one of the best disinfectants for contaminated material next to boiling water is formalin. On the other hand, the virus is more resistant to phenol, to glycerin and to some other disinfectants than are some bacteria, so glycerin or weak phenol is used in preserving the vaccin and in ridding from contaminating bacteria decomposed brains sent in for diagnosis.

The resistance of the virus to drying and heating has also been made use of in vaccin preparation. Thus, slow drying at a moderate constant temperature (about 20°C.), as used in preparing vaccin, causes a gradual loss of virulence. Very rapid drying at any temperature up to 36°C. preserves much of the virulence. At 60°C. the virus is killed in five minutes. The virus remains virulent for a long time when kept in a cold, dark place, protected from the air.

Many have attempted to determine the morphologic agent of rabies, but so far evidence is still lacking for complete proof. The structured bodies known as Negri bodies, after Negri (1903), which are found chiefly in the large nerve cells of the nervous system, have been studied extensively by many investigators, among them Williams (1904–1913) and Williams and Lowden (1906). Williams agreed with Negri that they are probably protozoa and the cause of rabies, and gave them the name of *Neuroryctese hydrophobiæ*. The evidence upon which this conclusion is based may be summed up as follows:

1. The bodies show a distinct morphologic cycle indicating growth and multiplication; i.e., small, rounded or oval plasin-staining granules; each containing a minute chromatin-staining granule; similar forms in twos or groups; larger forms containing a definite central or eccentric chromatin-staining mass with smaller chromatin-staining masses arranged in a ring about it; evidence of division of these larger forms as well as of the small ones, both by segmentation and by budding, phenomena which account for the appearance in the same cell and at the same time of both large and small forms, and also help to account for the rapid spread of the organism and for forms small enough to pass certain filters.

2. The bodies are found in all parts of the tissues proved infectious in susceptible animals. They are distinguished first as extremely minute forms in large nerve cells, before symptoms appear, i.e., on the fourth day in rabbit fixed virus infections and on the seventh day in rabbits inoculated with street virus; thus they are found early enough to account for the infectivity of the host tissue.

Several other explanations of the nature of these bodies have been given, the more likely of which are (1) that the specific microörganisms are the small chromatin masses seen within the plastin-staining (cell-reaction) portion of the bodies; (2) that they are degenerations due to the cell reaction caused by the rabies toxin, which may or may not contain the organisms.

Whatever their nature, the morphologic specificity of these bodies has been accepted, therefore their practical use in diagnosis is established.

Pathology.—Rabies germs soon after entrance into the system are supposed to pass chiefly, if not exclusively, along the nerve fibers to the brain, and certain glands. They progress so slowly along the course of the nerve that they do not disturb its function. When they reach the large nerve cells they enter these and continue their growth, first stimulating and then destroying the cells.

On gross autopsy no specific changes are seen. This fact in itself may be considered characteristic. General changes due to congestion may show in the central nervous system, the salivary glands, the thyroid, the pancreas, and the suprarenal capsules. Pin-point hemorrhages and minute areas of softening may be seen in them on section. All mucous membranes may show catarrhal inflammation. The condition of the stomach in dog may be of aid in diagnosis. It is usually empty of food but may contain a mixture of foreign substances such as pieces of cloth, hair, leather, wood and straw.

Certain changes showing in microscopic sections are more important as an aid in diagnosis. The "rabic tubercles," first described minutely by Babes (1892), are the first lesion that is seen on microscopic examination of stained sections of the spinal cord from a case of rabies. These consist of groups of small spheroidal cells surrounding many of the blood-vessels and the large nerve cells, especially marked in the anterior and posterior horns. These groups are not always found in cases of rabies, and when present are not developed until late in the disease, so they are of limited use in diagnosis. Another important pathological change was found by Van Gehuchten and Nelis (1900) in the cerebrospinal ganglia. This is the disappearance of many of the large nerve cells and in their places groups of small infiltrating spheroidal cells, and proliferated cells of the capsules. These changes may appear quite early, so, though not absolutely specific, may be of help in diagnosis. The Negri bodies, have already been described and it is upon their presence alone that most laboratories depend for their diagnosis.

Symptomatology.—**Incubation.**—The incubation period varies, it is longest in man, and is shorter in cases infected on the shorter nerve trunks. The number and depth of bites does not appear materally to the affect incubation time. Anything that lessens vitality, shortens bation.

The time from the occurrence of the bite to the appearance of the first symptoms in man is rarely earlier than 12 days or later than 90. The limits given are eight days and several years. The average limits are from three to eight weeks. Cases reported as occurring one year or more after the bite have not absolutely reliable data.

In dogs the limits are from eight days to one year, with an average of two to eight weeks. Cats and swine generally have a slightly shorter incubation, while cattle and horses have a slightly long one.

The symptoms may be divided broadly into two general groups or stages: (1) Those of cerebrospinal excitation or irritation (furious rabies); (2) those of nerve-system degeneration (dumb rabies). Many cases show mixed symptoms, and a few are quite atypical. It is important to know the symptoms in the dog as well as in human beings in order to decide whether or not the preventive treatment should be given.

Symptoms in the Dog.—*Furious Rabies.*—The character of the animal usually becomes changed; he may be either more affectionate or less so. Since the sputum of a dog may be virulent for 15 days before he shows symptoms, we should beware of his licking especially if there is a question of a fresh wound, even a scratch or hang-nail. The appetite may be abnormal, and the dog may begin to be morose and to bite at things and animals, especially at dogs. He may seem better, then he becomes worse, and soon spasmodic seizures begin. His bark may become characteristically altered to a low howl followed by an irregular series of low-pitched barks between unclosed jaws. He generally eats and drinks as long as he can. His saliva usually drops, but he may not "froth at the mouth." This stage passes gradually into that of paralysis. Pupils are irregularly dilated, spasms become less and muscles get weaker until death. Duration from four to eight days.

Dumb Rabies.—In about one-fifth of the cases the first symptom is paralysis, usually of the lower jaw ("drop-jaw"). One should beware of a dog with a "bone in his throat," and should remember that though the animal does not bite, its sputum may be virulent, therefore contact with a recent wound should be avoided. The rest of the body quickly becomes paralyzed, and death follows in about the same time as in furious rabies.

Symptoms in Human Beings.—*Furious Rabies.*—The great majority of the cases in humans are of this type. For about 48 hours there are usually indefinite nervous symptoms such as a sensation of constriction in the throat, or of difficulty in walking or breathing, or of precardial anxiety, or of neuralgic pains. Several cases showing pronounced distress for a much longer time before definite symptoms appear have been reported. During this period the temperature is slightly increased (38 to 39°C.). The fear of water usually develops early, owing to painful spasm from attempt to swallow. Characteristic spasms may be caused by a draft of air (aerophobia) or loud noises (hyperacusis). The attacks usually occur intermittently except in the very severely infected cases. At about 48 hours the excitement increases and is usually accompanied by hallucinations,or even mania; though usually no attempt is made to injure others. The mind remains clear between attacks. Vomiting usually occurs. The voice may be very hoarse, but there is no barking. The eyes may show photophobia, nystagmus, strabismus and unequally dilated pupils. The patient may die suddenly at any time during this stage, but he usually passes in about one to four days into the paralytic stage, with muscles relaxed, jaw dropped, ropy saliva flowing, and he becomes comatose and dies in about 2 to 18 hours. Just before death the temperature may become very high (42 to 44°C.).

Paralytic (Dumb) Rabies.—This type of rabies is less frequent in human beings than in lower animals. Its recognition is particularly necessary so that it may be differentiated from the paralyses which occur exceptionally during or just after the Pasteur treatment. The extremities feel heavy and numb; then quickly a condition of ataxia and progressive paralysis develops. Death occurs in from two to eight days from paralysis of the heart.

Diagnosis.—Clinically, the chief conditions in which a differential diagnosis may be necessary are hysteria (lyssophobia), delirium tremens, tetanus, and any toxin or poisonous drug affecting the brain primarily.

If exposure to infection from a rabid animal can be ruled out and if there is no reflex irritability, rabies may be eliminated. In hysteria, the symptoms are amenable to suggestion. In tetanus the spasms are tonic instead of clonic. Malaria affecting the brain has been reported as simulating rabies. Here the finding of the malarial organisms in the blood and the control of the symptoms by quinine will clear up the diagnosis.

Diagnosis of the Biting Animal.—After having received a bite the first question is, did the biting animal have rabies at the time of biting? If the case has been bitten by an animal that cannot be diagnosed clinically, the laboratory tests for the diagnosis of the animal must be relied upon: These are (1) the microscopic test, (2) animal inoculation.

The microscopic test consists in the demonstration of the Negri bodies. The rapid spread method recommended by William (1904) is generally used. If Negri bodies are found, the case is considered one of rabies. Infrequently a brain does not show these typical bodies, yet produces rabies in test animals. All such brains if in good condition when they are received for examination show suspicious small forms, and are treated as rabies, pending the result from the animal inoculation. So the percentage of failures todiagnose by the spread methodis very small.

In New York City Health Department, the material sent in for diagnosis is handled as follows:

1. Spreads are made of the brain material by pressing between a glass slide and a cover-glass a small, thin section of the gray matter from each of these parts of the brain: (*a*) The cerebral cortex, (*b*) Ammon's horn, (*c*) the cerebellum. The material is spread along the slide by moving the cover-glass down with the finger. The amount of pressure to be used must be learned by experience.

2. When partly or completely air-dried the smears are fixed for about 10 seconds in neutralized methyl alcohol (c.p.) containing 0.1 per cent. of picric acid. The slide is then blotted with fine filter paper and stained as follows:

Saturated alcoholic solution of fuchsin	0.5 part
Saturated alcoholic solution of methylene blue	10.0 parts
Distilled water	30.0 parts

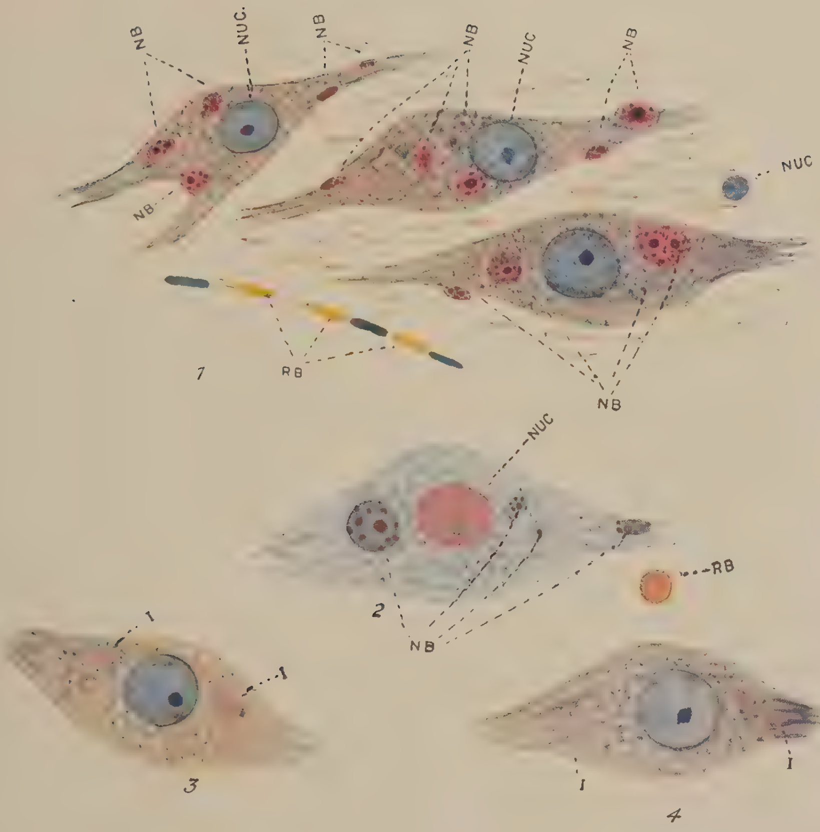
The stain is poured on the smear which is held over the flame until steam arises and is then washed in tap-water and blotted. The Negri bodies (Plate I) are stained a magenta color with blue granules, the never cells blue, and the red-blood cells yellow or salmon color. Giemsa's stain also gives good results. If no Negri bodies are found smears are examined from other parts of the brain. Then, if none are found an emulsion is made in 10 c.c. normal salt solution of a piece the size of a bean from the three parts of the brain, from which an intracerebral inoculation (0.25 c.c.) is made into each of three guinea pigs. Some of the brain is preserved in sterilized neutral glycerin in the ice-box for later tests if necessary. By this method contaminated brains are rid of their extraneous organisms, while the brain continues to contain active rabies germs for several months. If the brain is decomposed when received, the emulsion preserved in glycerin is inoculated after two weeks, unless positive results have been gotten from the first inoculation. Sections may be made, but usually they give no more definite evidence than do the spreads. The serologic tests—complement fixation, precipitation and agglutination—have not yet given satisfactory results. The inoculated guinea pigs are kept under observation for at least two months. If the animal was rabid they usually show symptoms in from 9 to 12 days.

Prognosis.—After symptoms appear in human beings no instance of recovery has been proved to occur. The mortality percentage after bites has already been given.

Treatment.—The most effective treatment of cases infected with rabies virus is that of prophylaxis by means of a specific vaccin. The good results depend upon the fact that the virus becomes active only after a comparatively long incubation period. Neither antiserum nor any other treatment has given any help towards cure after the symptoms appear. The few cases reported as cures in man at this stage lack proof that the diagnosis was correct. It has been shown, however, that experimental animals may occasionally, after showing symptoms, recover spontaneously, therefore the possibility of the same thing occurring in man cannot be ruled out; and one may still hope to discover a cure for the disease at a late stage, if not from a specific serum, perhaps from a special drug, though quinin has not fulfilled its promise, neither has salvarsan nor any other drug so far tried. The only treatment used after the disease has developed is symptomatic and is directed toward the spasms. Enemata of large doses of chloral hydrate and the bromides may be given. Hypodermatic inoculations of hyosine hydrobromide may be given in $\frac{1}{100}$ gr. doses. Cocaine may be administered to the larynx. Finally, chloroform may be used to control severe spasms.

Prophylactic treatment may be both local and constitutional. The *local* treatment consists in inducing bleeding, then cleansing the wound with any fluid antiseptic solution. After that, *and most important, the wound should be thoroughly cauterized with fuming nitric acid.* It this cauterization can be done within 24 hours after the bite, and the

PLATE I



A. W. WILLIAMS, DEL.

Nerve cells in spreads from Ammon's horn. Magnification 1200 diameters. Figs. 1 and 2 from dog "street rabies" show "Negri bodies" (NB); Fig. 3 from non-rabic cat, and Fig. 4 from dog distemper show indefinite inclusion (I) that might be mistaken for Negri bodies by the inexperienced. Negri bodies are structured, more intensely staining, and more refractive. Figs. 1, 3, and 4 are stained by fuchsin-methylene-blue mixture, which stains Negri bodies (NB) red with blue granules, nucleus (NUC) of nerve cells blue, and red-blood cells yellow (RB). Fig. 2 is stained by Giemsa's mixture, which stains Negri bodies a robin's egg blue with red granules, nucleus of nerve cells red, and red-blood cells salmon pink. (From Park and Williams, Pathogenic Microörganisms, Published by Lea and Febiger, 1920.)

wound has not been too deeply lacerated, the case may be protected, since the virus travels so slowly. Tincture of iodin cannot be trusted to act as well as does fuming nitric acid. Nor can any other chemical disinfectant. Even the actual cautery is not as good as the strong nitric acid though this stands next in order of merit.

The *constitutional treatment* consists in the use of the specific vaccin. In order to decide whether or not it is necessary to give this expensive and time-consuming treatment the diagnosis of the biting animal, as we have said, should be known. This is often difficult to determine. The suspected animal may have indefinite symptoms or may have been killed too early, or may be a stray who has disappeared, or the brain may be in too bad a condition for microscopic diagnosis. Unless rabies can be ruled out we must be guarded in advising no treatment, especially in communities where cases of rabies have been reported.

Treatment should be advised, therefore, under any of the following conditions: (1) When the biting animal gives definite evidence of rabies. (2) When the animal cannot be found just after biting. This is always a suspicious symptom, when no facts can be learned to account for it. (3) If the biting animal has been killed too early to give clinical or microscopic evidence of rabies, or if its brain is in too bad a condition for immediate diagnosis, pending the results of inoculation of test animals. If these test animals show no symptoms in 12 days the treatment may be stopped, to be begun again if the animals show symptoms later. (4) If the animal is apparently healthy or has only suspicious symptoms, it should be kept under observation for at least three weeks, and treatment should be begun if suspicious symptoms appear or become more marked. (5) If the animal has been killed and no evidence can be obtained for or against rabies, treatment should be advised in areas where rabies is prevalent. (6) If anyone has been exposed only to suspicious animal's saliva, unless infected fresh cuts or abrasions can be ruled out, treatment should be advised.

The specific preventive treatment of rabies, known as the *Pasteur treatment*, is still used with modifications all over the world. Pasteur found that when he passed the virus obtained from dogs—"street virus"—successively through certain species of animals (notably rabbits) by subdural inoculations, it became markedly increased in virulence for these animals shown both by the shortened incubation period and the smaller doses required to produce death. After many successive passages through rabbits (about 30) the virus in rabbits dying from the infection would bring down fresh rabbits with the disease in a fixed time (about seven days). Pasteur called this virus fixed virus, and he used this to obtain a regulated series of weaker doses by drying at a constant temperature.

The rabbits are inoculated both for the production of vaccin and the enabling of a diagnosis of suspected material in the following way:

The skin over the point of inoculation is washed with a 5 per cent. phenol solution. A ¼ in. incision is then made through the skin back of the eye on one side of the median line, the skin is held apart and a small opening is made with a guarded sharp-pointed instrument through the skull bone just large enough to admit the fine short (¼ in.) hypodermic needle of the syringe containing the emulsion (0.2 c.c.) which is inoculated intracerebrally. The small wound may be covered with a little cotton and collodion. Rabbits inoculated for obtaining vaccin are killed on the seventh day after inoculation and the spinal cords are removed aseptically by the Oshida method

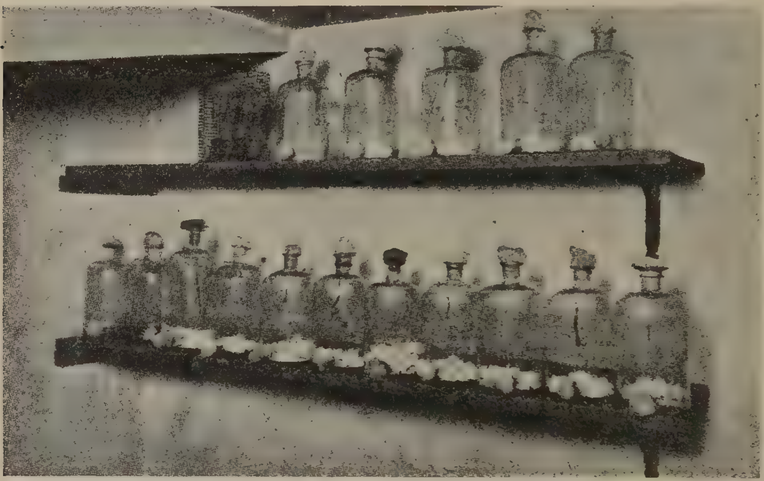


FIG. 29.—One corner of constant temperature room showing drying bottle containing fixed virus cords being prepared for vaccine. (Park and Williams.)

and dried in sterile aspiration bottles over caustic potash (Fig. 29) at 20°C. (7°F.) for successive days, so that a series of cords are obtained from one day old to eight days old (present modified method). After 24 hours drying the cord is known as one day cord, after two days, as two day cord, etc. The patients are inoculated subcutaneously daily, with emulsion of definite quantities of these cords, according to a scheme like the following:

Twenty-one Day Scheme of Pasteur Treatment Started May 7, 1914

Day	Days	Cord dried, face cases	Number of injections	Adults	Children	
					8 to 10 years	1 to 5 years
1	8 and 7 and 6	8 and 7 and 6	2	3 c.c.	3 c.c.	3 c.c.
2	8 and 7 and 6	8 and 7 and 6	2	3 c.c.	3 c.c.	3 c.c.
3	5 and 4	5 and 4	2	3 c.c.	3 c.c.	3 c.c.
4	5	5	1	2 c.c.	2 c.c.	2 c.c.
5	4	4	1	2 c.c.	2 c.c.	1.5 c.c.*
6	4	4	1	2 c.c.	2 c.c.	1.5 c.c.*
7	3	4	1	2 c.c.	1.5 c.c.*	1 c.c.*
8	3	3	1	2 c.c.	1.5 c.c.*	1 c.c.
9	5	2	1	2 c.c.	2 c.c.	2 c.c.
10	4	4	1	2 c.c.	2 c.c.	2 c.c.
11	4	4	1	2 c.c.	2 c.c.	2 c.c.
12	3	3	1	2 c.c.	2 c.c.	1.5 c.c.*
13	3	2	1	2 c.c.	2 c.c.	1.5 c.c.*
14	4	4	1	2 c.c.	2 c.c.	2 c.c.
15	4	4	1	2 c.c.	2 c.c.	2 c.c.
16	3	3	1	2 c.c.	2 c.c.	1.5 c.c.*
17	3	2	1	2 c.c.	2 c.c.	2 c.c.
18	4	4	1	2 c.c.	2 c.c.	2 c.c.
19	4	4	1	2 c.c.	2 c.c.	2 c.c.
20	3	3	1	2 c.c.	2 c.c.	2 c.c.
21	3	2	1	2 c.c.	2 c.c.	2 c.c.

* Face cases receive adult doses.

Each dose contains 0.5 cm. of the indicated cords.

Pieces of cord cut off at any time and put into glycerin will retain about the same strength for several weeks. Phenol 0.25 per cent. is added as a preservative in sending treatment by mail. The idea of the New York City Health Department that treatment could be sent quickly by mail was carried out by most other laboratories where rabies vaccin is prepared.

A number of other methods of attenuating the virus for dosage have been recommended, among them are dilution (Högyès, Babes, Philips), carbolic acid (Fermi), rapid drying in cold (Harris), formalin and dialysis (Cumming), serum-virus mixture (Marie). Remlinger, Marie and others claim that dogs inoculated intra-peritoneally into the anterior chamber of the eye with only one injection of an unsaturated serum-virus mixture are protected against rabies. Umeno and Doi also report protection in dogs after an inoculation of their vaccin. Very good results continue to be reported by the Harris method.

The nature of the antibodies in rabies serum is still not well understood. Some claim that specific antibodies have not been demonstrated. They have found that the serum of certain animals which are more or less refractory to rabies possesses a small amount of rabicidal strength.

Contra-indications for Treatment.—There are no specific contra-indications. The treatment may cause only slight local discomfort and erythema. Very occasionally cases of slight neuritis and transient paraplegias and paralyses of various parts of the body have been reported. Extremely rarely a case of marked paralyses with death has been reported. Fielder (1916) reported our very few cases of paralyses and gives a summary of others. The mortality in these cases is less than 1:10,000. The largest number of fatal cases have occurred after hyperintensive methods. The people so affected seem to have an unusual susceptibility.

Results of Antirabic Treatment.—On the whole the results are markedly good, but the statistics have not been kept with enough uniformity or minuteness to be able to determine the comparative worth of the different methods of treatment. In getting statistics for mortality from rabies after treatment, 15 days must be allowed for time to establish immunity by the treatment. Any deaths that occur within 15 days after the last treatment are considered to have been too severely infected or too susceptible or infected with too virulent a virus to have given time for the production of immunity by the treatment. Two figures are therefore given in mortality statistics: The absolute mortality and the corrected mortality, i.e., that occurring beyond the 15 day limit.

The physician should remember that in keeping the statistics, the following details should be known and recorded: (1) Diagnosis of the case (*a*) rabies, (*b*) probably rabies (*c*) questionable, (*d*) not, rabies, (*e*) nothing known; (2) method of making diagnosis, (*a*) by animal inoculation, (*b*) by microscopic examination, (*c*) by clinical diagnosis; (3) site and character of bites (number, depth, laceration, protected by clothing, etc.); (4) time elapsing between bite and beginning of treatment; (5) method of treatment; (6) complications, particularly paralysis; (7) character and time of death.

In New York at the Health Department laboratories where the results compare favorably with those of other laboratories, 6997 cases infected with rabies were treated from 1906 to 1919 inclusive, with a total mortality of 0.39 per cent. and a corrected mortality of 0.12 per cent.

Immunity.—In human beings, the immunity produced by the vaccin treatment lasts a variable time. It may not last longer than 14 months. Dogs may be completely immune (Marie) 18 months after treatment.

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CHAPTER CLI

FOOT-AND-MOUTH DISEASE

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Synonyms.—Aphthæ epizootical, epidemic stomatitis, aphthous fever.

Definition.—Foot-and-mouth disease is an acute infectious, very contagious disease of domestic animals, especially cattle and hogs, and is communicable to man. It is characterized by the appearance of a vesicular eruption in the mouth and pharynx, and on the skin, especially in the interdigital spaces, slight fever and marked prostration.

Occurrence.—While the disease more commonly affects cattle and hogs, it has also been seen in sheep, the goat, dog, cat, horse, buffalo, camel, llama, giraffe, antelope and elk. It may be transmitted from these animals to man. The disease occurs in epidemic form and spreads rapidly among the domestic animals. Epidemics affecting large numbers of animals have been reported in Germany, France, Austria, Hungary, Poland, Great Britain, Holland, Roumania, Belgium, Switzerland, Argentina, United States, Asia, and Africa. Australia is free from the infection. In man the disease is usually sporadic, in persons coming directly in contact with diseased cattle, or in children from drinking milk from goats and cows suffering from foot-and-mouth disease. Robinson reports an epidemic of foot-and-mouth disease in Devonshire. In one week 205 persons contracted foot-and-mouth disease. Demme reports a case of twins both of whom developed foot-and-mouth disease from goat's milk. One died after seven days illness, the other recovered. Foot-and-mouth disease occurs much more frequently in summer than in winter, and it occurs more frequently in children between the tenth and thirteenth month of life.

Etiology.—The cause of foot-and-mouth disease is undoubtedly a specific microörganism of the ultra microscopic or filterable virus variety. While the organism causing the disease has not been isolated, it can be classed as an acute infectious disease because of its nature and transmission. The virus may be passed through a fine Berkefeld filter without losing its virulence. The infectious virus exists in the vesicles of the mouth and feet, in the secretions from ulcers, in the saliva, in the nasal discharge, in the milk, in the blood and lymph, and possibly in the feces and urine. The virulence gradually diminishes during the course of the disease; by the tenth day the secretions are not infectious. The virus is readily killed by heat. Virus which may be in the milk from infected cattle is destroyed by pasteurization at 60°C. for 20 minutes.

Virus is no longer infectious after having been treated with 1 per cent. phenol or 2 per cent. formalin for one hour.

Infection may occur by directly coming in contact with the virus, as in the handling of cattle or hogs in shipping and slaughtering. Milkers and dairymen are frequently infected through direct contact. More frequently children are infected by use of milk, butter, cheese, buttermilk and whey from infected cattle or goats. Foot-and-mouth disease has been transmitted to calves through small-pox virus, and one or more outbreaks have been attributed to this cause. No case in man has been caused by infected small-pox virus. Rosenau states that it is impossible to transmit foot-and-mouth disease to man through small-pox virus. One or more epidemics of foot-and-mouth disease in cattle have been attributed to the use of hog cholera serum which was infected with foot-and-mouth disease. It seems to be necessary to get the virus on the mucous membrane in order to contract the disease, though it is possible to be infected through trauma in the skin. One attack reduces the susceptibility for a short time. No definite immunity is produced.

Pathology.—Vesicles of the mouth and skin begin with hyperemia, serous infiltration; later the exudation becomes cloudy from the migrated leukocytes. Frequently there is pus formation from secondary infection. In the mouth, the vesicles soon rupture, forming superficial ulcers. The ulcers extend in many cases into the pharynx and also into the larynx. In man the eruption is usually limited to the mouth and throat, dorsal surfaces of hands and more rarely the feet. In cows it is frequently seen also on the udder and teats. In the fatal cases, the apthous condition had extended into the respiratory tract, causing extensive lesions of the lungs. Hemorrhages were seen on some of the serous membranes, especially the pericardium, and extensive ulceration of the gastro-intestinal tract was found.

Symptoms.—The incubation period varies from 2 to 14 days. The disease usually begins with chill followed by a rise in temperature. In children there is usually gastro-intestinal catarrh. There is loss of appetite, general feeling of depression, mucous membrane of the mouth and pharynx becomes dry and parched. The tonsils and lymphatic glands of the neck are usually enlarged. After two or three days, white epithelial spots are seen on the mucous membrane of the lips, gums, cheeks, and sides of the tongue. Surrounded by an areola. The tongue is usually coated and red along the edges. The conjunctiva is frequently swollen and congested. Discreet vesicles appear on the dorsal surfaces of the hands and feet, and occasionally on other parts of the body, as nose, face, ears, knees and buttocks. The bases of the vesicles on the skin are reddish and are not well defined. The skin eruption resembles somewhat erythema multiforme, but in foot-and-mouth disease the vesicles are somewhat smaller. In the latter disease they vary from the size of a pin head to that of a pea. The vesicles in the mouth soon rupture, forming ulcers; those on the skin pass from the vesicular to the pustular stage, then heal without scarification. The ulcers are frequently rather persistent and there is profuse salivation. Swallowing is difficult, and the increased flow of saliva makes it imperative to empty the mouth frequently. Vomiting is not uncommon. In children diarrhea is frequently seen. Pains in the extremities, headaches, dizziness, vomiting, diarrhea, and general malaise are frequently seen. The disease usually runs a mild course in man, except in young and weakened children, and then there is usually some complication. The course of the disease is usually from three to six weeks.

Treatment.—Prophylaxis is important. As soon as an outbreak occurs, the Federal Government makes a thorough investigation. All diseased cattle are killed and any suspects quarantined. The killed cattle are burned or buried. Interstate shipment of cattle is stopped. Thus by vigorous and drastic measures the disease is soon stamped out. It is an expensive procedure, but it is much the cheapest method in the end.

The prevention of foot-and-mouth disease in man is similar to the prophylaxis in other contagious diseases. The patient should be isolated and quarantined. Persons with cuts or abrasions should not be allowed to milk diseased or suspected cattle. Persons who handle diseased cattle should thoroughly disinfect their hands and their clothing should be thoroughly fumigated or burned. During an epidemic and whenever there is any possibility of cows being infected all milk should be pasteurized or boiled, including the butter fat. Meat from all animals should be thoroughly cooked when foot-and-mouth disease prevails.

The curative treatment is symptomatic and dietetic. The use of serums has not been very successful. The diet should be light and usually liquid. Laxatives, such as rhubarb and magnesia, have been recommended. The ulcers of the lips and mouth may be treated with nitrate of silver, tincture of chlorid of iron, or 1/3 per cent. solution of permanganate of potash. The glycerite of phenol applied with absorbent cotton frequently gives good results. A favorite gargle is made from a 2 per cent. solution of chlorate of potash. The skin eruption seldom needs treatment.

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CHAPTER CLII

ERYSIPELAS

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Synonyms.—Latin: Erysipelas. Popular: St. Anthony's fire, the rose. French: Érysipèle. German: Rothlauf, erysipel. Italian: Risipola. Spanish: Erisipela.

History.—The history of erysipelas like so many other diseases dates back to Hippocrates. His reference to the disease in the "Epidemic Diseases," Book 3, Sections 3 and 4, is as follows:

"Early in the spring, along with the prevailing cold, there were many cases of erysipelas, some from a manifest cause, and some not. They were of a malignant nature, and proved fatal to many; many had sore-throat and loss of speech. There were many cases of ardent fever, phrensy, aphthous affections of the mouth, tumors on the genital organs; of ophthalmia, anthrax, disorder of the bowels, anorexia, with thirst and without it; of disordered urine, large in quantity, and bad in quality; of persons affected with coma for a long time, and then falling into a state of insomnolency. There were many cases of failure of crisis, and many of unfavorable crisis; many of dropsy and of phthisis. Such were the diseases then epidemic. There were patients affected with every one of the species which have been mentioned, and many died. The symptoms in each of these cases were as follows:

"In many cases erysipelas, from some obvious cause, such as an accident, and sometimes from even a very small wound, broke out all over the body, especially in persons about 60 years of age, about the head, if such an accident was neglected in the slightest degree; and this happened in some who were under treatment; great inflammation took place, and the erysipelas quickly spread all over. In the most of them the abscesses ended in suppurations, and there were great fallings off (sloughing) of the flesh, tendons, and bones; and the defluxion which seated in the part was not like pus, but a sort of putrefaction, and the running was large and of various characters. Those cases in which any of these things happened about the head were accompanied with falling off of the hairs of the head and chin, the bones were laid bare and separated, and there were excessive runnings; and these symptoms happened in fevers and without fevers. But these things were more formidable in appearance than dangerous; for when the concoction in these cases turned to a suppuration, most of them recovered; but when the inflammation and erysipelas disappeared, and when no abscess was formed, a great number of these died. In like manner, the same things happened to whatever part of the body the disease wandered, for in many cases both forearm and arm dropped off; and in those cases in which it fell upon the sides, the parts there, either before or behind, got into a bad state; and in some cases the whole femur and bones of the leg and whole foot were laid bare. But of all such cases, the more formidable were those which took place about the pubes and genital organs. Such was the nature of these cases when attended with sores, and proceeding from an external cause; but the same things occurred in fevers, before fevers, and after fevers. But those cases in which an abscess was formed, and turned to a suppuration, or a seasonable diarrhea or discharge of good urine took place, were relieved thereby; but those cases in which none of these symptoms occurred, but they disappeared without a crisis, proved fatal. The greater number of these erysipelatous cases took place in the spring, but were prolonged through the summer and during autumn.''

The early writers confused a great many different conditions with erysipelas very much as the practitioners of today, and indeed it is difficult to draw hard and fast lines around a disease which is an inflammation of the lymphatic vessels and which often shows a distinct tendency to spread to the subcutaneous and other tissues. The French very wisely have used the term "*érysipèle legitime*" to cover the cases in which the classical picture is more or less closely adhered to. The various Arabian physicians and the Greek and Roman writers were familiar with the disease and gave descriptions of it, mixing it, as has been said, with other inflammatory processes. Galen first drew the line between erysipelas and phlegmon and held that the disease was in some way influenced by the weather, but had its origin in the biliary secretion, and this biliary theory prevailed in medicine until 1840, when Henle published his studies.

Henle changed the trend of thought regarding erysipelas in that he credited the lowest vegetable organisms as being the probable cause of contagious diseases, and Werenher in Germany, and Velpeau and Trousseau in France, emphasized the dependence upon external injuries and stated more or less definitely that the disease was contagious. Volkmann, in 1869, thought that the disease was due to a local disturbance dependent upon the influence of a special poison, and this was soon followed by a number of observers who believed that the disease was due to some organism. Hüter and Hervieu, in 1870, described microbes, but there is no certainty that the organisms they saw were the streptococcus with which we are familiar at the present time. In 1886, Bouchard described diplococci and organisms occurring in short chains, and Pasteur and Doleris, in 1880, confirmed these observations, and Lukomsky, Bilroth and Ehrlich all were of the opinion that the disease was caused by organisms, but it remained for Fehleisen in his article *Ueber Erysipel*, in 1882, to demonstrate that the disease was caused by a streptococcus. He described the organism as found only in the lymphatic channels or spaces, and not in the other blood-vessels or the skin and was able to grow the organism from pieces of tissue removed from the diseased parts. Fehleisen named the organism streptococcus erysipelitas, but it was subsequently shown by Petruschsky that streptococci from other sources could cause the disease and the more recent bacteriologic studies make no distinction between the streptococcus pyogenes and the organism described by Fehleisen.

Erysipelas of the newborn is supposed to date back to Hippocrates, but it was not until the eighteenth century that special attention was paid to this disease. Mauriceau, in 1712, believed it to be due to a fermentation of the blood accumulated around the umbilicus after the ligation of the cord. Heberden, in 1807, in his "Epitome of the Diseases of Children," gives the following description of the erysipelas of children:

"A disease bearing some affinity to the erysipelas sometimes attacks children in the first month, especially those who are born in public hospitals. The mildest species of it arises sometimes in the fingers and hands, sometimes in the feet or ankles; where it is presently followed by ulceration. There is a worse kind, which begins near the pubes, from whence it spreads upon the belly and thighs. Wherever it is formed the skin becomes livid and hard: there is not much swelling, but the parts which are affected by it have a tendency to gangrene, especially the scrotum in boys, and at the same time the penis is distended. It often proves fatal in a few days. When the body has been opened after death, the intestines have been found glued together, and covered with coagulable lymph."

Later Billard and Bouchut and Trousseau called attention to the fact that erysipelas of the newborn frequently followed puerperal infections of the mother and epidemics of both diseases are related by Lorain, by Hervieu and Meynet.

Etiology.—The Streptococcus pyogenes is practically always the cause of the disease. This organism is a minute coccus occurring in pairs and particularly in short serpent-like chains, as described by Cohn. The organism is easily stained by the usually aniline dyes and is not decolorized by Gram's method.

The Streptococcus pyogenes includes all streptococci that produce hemolysis and ferment dextrose, lactose, saccharose, and salicin, but not mannite. The organism varies from 0.4 to 1 micron in diameter and the colonies in the agar plates vary in size from a pin point to a pin head and are visible in about 12 to 30 hours. The organism also grows well in milk and other media. It does not live long outside the body, but in dried blood or pus may persist for several months at room temperature and even longer if kept in the ice-box.

The organism causing an erysipelatous lesion is not of necessity the Streptococcus pyogenes and in very exceptional cases may be caused by other organisms. A very good account of this is given by Reiche. Jochmann found a staphylococcus in a case which followed a furuncle on the nose, and Reiche described a fatal case coming on with pneumonia complicated by meningitis in which a staphylococcus was recovered from the skin. Von Leube and Neufeld have found the pneumococcus in typical lesions and Shomonerus and Reiche have found the pneumococcus in the skin lesions of a typical case of erysipelas complicating a pneumonia.

Pathology.—The organism gets into the lymphatics of the skin generally through an abrasion and is but rarely found in the capillaries. This limitation of the organism to the lymph capillaries in all probability explains the appearance of the skin in typical cases. The changes caused by the organism may be cutaneous or may go deeper and involve both the cellular tissue underneath as well as the skin, and in some cases there is a definite cellulitis. There is a cellulo-fibrinous inflammation in the corium and even in the deeper structures. The blood-vessels and lymphatics are congested and there are collections of polymorphonuclear leukocytes about the vessels, the cells of the skin show cloudy swelling and frequently necrosis and if there is vesicle formation the fluid contains fibrin and leukocytes.

Holmes has written an interesting article on the cases of erysipelas which follow infections of the nose, operations on the mastoid and sinus inflammations. He believes that the disease is facial in many cases from the fact that the skin gets inflamed from the upper air passages or ear, often from patients scratching the nose with the finger and so causing slight abrasions, and that the individual who has become practically immune to the organisms at the site of their original location is not immune to the same streptococcus when transplanted to another place, especially when the resisting power of the individual is for any reason reduced.

The disease may be transferred by direct contact, from fomites towels, instruments, or unclean hands. The organism has been recovered from the air of wards occupied by erysipelas patients. In infancy the disease is usually especially virulent and the site of infection is generally the umbilicus, although head infections are by no means rare.

Erysipelas is principally a disease of the temperate zone, but epidemics have been noted in the far north and in the various tropical countries, although, as a rule, these latter seem to be remarkably free from the disease. It occurs sporadically or in epidemics; most of the epidemics have been in hospitals or in institutions or on ships. The conditions of hospital wards with the over-crowding of patients and the lack of cleanliness and all the other horrors that prevailed in institutions where the sick were housed until recent times, make one wonder why erysipelas epidemics were not even more common than they were. Hirsch gives an account of some of the epidemics and calls particular attention to some which occurred in the United States, starting about 1822 and prevailing up to recent times, but particularly so from 1841 to about 1860, during which time the disease was described as a pandemic. The climate does not seem to influence the disease as far as its general appearance is concerned and there is no racial immunity, although the disease may be easily overlooked in the dark-skinned peoples.

Incubation Period.—The incubation period varies from three to seven to ten days.

Symptoms.—The disease in children may be divided into two distinct classes: As it occurs in the newborn and as it is seen in older children.

In Older Children.—The disease usually follows a slight abrasion or an injury or a surgical operation and in some instances there is no history of anything definite. J. Lewis Smith gives a point of commencement in 58 cases as follows:

Arm vaccination	17
Vulva	13
Leg	7
Face	6
Male genitalia	3
Ear	1
Elbow	1
Shoulder	1
Buttocks	1
Foot	1

Thus it will be seen that facial cases are rare, 1:9, and the disease rarely extends to the face from other parts.

Occasionally there are prodromes lasting from a few hours to a few days and at other times the onset of the disease is rather abrupt. If the prodromes are present they consist of indefinite symptoms, loss of appetite, headache, restlessness, general malaise, and fever, and, in some instances, there is sore throat and cough. Sometimes there is a chill and high fever. If there has been an injury to the skin there is slight redness at this point and then there is within the first 24 hours a typical erysipelatous appearance. The skin is red and edematous and the surface generally smooth and tense. Here and there there may be small vesicles caused by an accumulation of inflammatory exudate under the epidermis. The disease spreads gradually, the spreading edge being sharply outlined and definitely raised above the adjoining normal skin. When the disease occurs about the head and face or about the genitalia there is usually very marked swelling and edema. The swelling about the face may be so marked as to render the patient unrecognizable. The adjoining lymph-nodes are always enlarged, but this is generally obscured in the swelling.

There are a number of different forms of the disease. In young children it may show no tendency to come to an end but migrate here and there over the body (erysipelas migrans). In some there may be a very definite tendency to form vesicles (erysipelas vesiculorum), and in some pustular formation is the predominating feature (erysipelas pustulosum). In children gangrene is not uncommon (erysipelas gangrenosa). Not infrequently the disease influences the cellular tissue, the so-called phlegmonous erysipelas, and sometimes there may be extensive abscesses in the subcutaneous tissue and at other times multiple smaller ones.

In some children the disease shows a distinct tendency to relapse. The child recovers and then after a short intervening period the disease recurs. This may happen a number of times. When the lymphatics of the mucous membranes are involved the disease is sometimes described as erysipelas of the mucous membrane, although in many instances this is described under the heading of a streptococcus infection of the particular tissue involved. This condition has been described in the pharynx, eustachian tubes, larynx, trachea, and bronchii. The adjoining lymph-nodes are enlarged edema of the glottis is an infrequent, but an exceedingly serious complication.

J. Lewis Smith gives the length of time the disease lasts as follows: In all 16 cases:

First week	2
Second week	6
Third week	5
Fourth week	1
Fifth and sixth week	2

with an average duration of 15 days.

Erysipelas in the Newborn.—Erysipelas neonatorum is, fortunately, a somewhat more rare affection than in the earlier days when less attention was paid to the hygiene of the newly born. It generally comes on a few days after birth, although it may occur 10 or 15 days after and cases may be seen at any time during infancy. The sexes are about equally affected in early infancy, whereas in later childhood the preponderance of cases occurs in boys. The disease in the newly born usually starts from an umbilical infection. It may follow a circumcision or a vaccination. It may occur about the face or head, particularly from forcep injuries. In former days the disease was exceedingly common when the mother had puerperal infections and this is still an occasional source of the disease. Petruschky has called attention to the fact that infection may also occur when the mother has an abscess or infection of the breast.

The disease comes on with great prostration and high temperature and great indisposition to take food, the child refusing to nurse. In some cases there is vomiting and diarrhea and convulsions are not uncommon. The child is profoundly ill and the mortality is exceedingly high. If the child gets well the disease gradually subsides, but there may be an edema persisting over the affected part for several weeks. In some of the cases the prostration is not so great, but even these often succumb. Death may take place from a convulsion, or by a sudden collapse, or by an extension of the disease to neighboring parts. Most commonly the extension is from the umbilicus to the peritoneum, but may also extend to the pleura, or there may be a pericarditis or endocarditis. In rare cases the inflammation may extend to the liver and cause a hepatitis which is accompanied with icterus; or, as in older children, there may be abscess formation. Sometimes abscess formation seems to be a rather favorable thing. Cases have been described in which small collections of pus were formed here and there, sometimes over a period as long as from four to six weeks, the infants fortunately recovering. In rare instances there may be phlebitis of the sinuses. One of the worst complications and also one of the most frequent is gangrene. This may take place on any part of the body and there may be multiple areas. Such cases have been described by Bouchut, Fredet and Vincent. Gangrene of the labia majora or of the scrotum, or the skin about the umbilicus are perhaps the most common. Sometimes the testes may be left entirely denuded from the destruction of the skin. Gangrene in young infants is almost invariably fatal, though not necessarily so.

Unusual forms of the disease may be noted, as by Macaulay, who described an afebrile case lasting three weeks and unfortunately dying; or by Milheit and Stevanin, who described cases with edema, but very little redness, and with marked swelling of the legs and multiple abscesses.

Antagonism of Erysipelas in Disease.—Interesting observations have been made by Gerhardt, Moran and others.. It is well known that malignant growths are sometimes influenced favorably by an attack of erysipelas, which led Fehleisen and also Busch to inject erysipelas organisms into patients with such tumors, and is also the basis of the Coley treatment. Other diseases are favorably influenced. Gerhardt has reported an interesting example of acute psychosis which disappeared during an attack of erysipelas to return as soon as the temperature became normal. Von Kopff has an instance of subacute joint rheumatism that was relieved by an attack of erysipelas. Moran relates a case of pneumonia that was cured by an intercurrent erysipelas; and Schmidt an attack of gonorrhea in a girl of three which disappeared when an erysipelas started on the fourth day of the disease.

Diagnosis.—The diagnosis of erysipelas usually presents no difficulties. The characteristic brawny, ridgelike, advancing margin of infiltration, with its sharp line of demarcation and its gradual spread is typical. There is always enlargement of the adjacent lymph-nodes, but this cannot always be made out. Sometimes examination of the exudate, if there is any, may be of assistance. In negroes and on the mucous membranes considerable difficulty may be experienced. The disease is most apt to be confused with eczema of an acute type with a great deal of redness, the eczema rubrum of some writers. This can usually be differentiated by the itching, the fact that the surface presents a scaly or moist appearance, and the margin is generally more or less diffuse, although not always. Erythema nodosum may also be mistaken for erysipelas, but the skin presents a much more dusky appearance and except in the very early stages, not the rose color of erysipelas. Anthrax infections have also been mistaken. Urticaria, particularly when it occurs in spreading erythematous patches with fever, may present some little difficulty, but the changeable character of the lesions and the presence of typical urticarial lesions on other parts of the body usually makes the diagnosis plain. The disease may also be confused with syphilitic pemphigus or the ordinary form caused by pyogenic bacteria. In the former there are practically always other lesions of the disease; in the latter, when due to a Streptococcus pyogenes, diagnosis may be practically impossible, but of no particular importance as far as the treatment is concerned. Intertrigo or chafing may be mistaken, but if it is borne in mind that this occurs in small spots or large areas and that the larger patches are usually excoriated and moist, the edges shading off into the normal skin, the line of demarcation is less abrupt and it lacks the brawny infiltration of erysipelas. Edema of the newborn and sclerema neonatorum should not offer any difficulties, and are usually accompanied with low temperature, rather than fever, and the skin is pale.

Prognosis.—The prognosis may be said to vary directly with the age of the patient. Kerley states that 95 per cent. of those occurring in the newborn are fatal and that under one year the mortality is 50 per cent. According to the observations of J. Lewis Smith, the average life of the fatal cases is 10 days. In 19 fatal cases the death occurred in the first week in 10, the second week in 5, the third week in 3, and in the fourth week in 1. A complicating peritonitis or gangrene is practically always fatal. Sprunt, studying adult cases, found contrary to the observations of earlier writers, that the streptococcus bacteremia was not unusual and that it had some relation to prognosis, inasmuch as those cases in which it was found frequently terminated fatally, whereas there were no deaths among the patients who had sterile bloods. In older individuals the leukocytosis equals the intensity of the infection so that the lower counts, except in the moribund, usually mean a good prognosis, whereas the higher ones, over 25,000, a bad prognosis. Where there is a gradual fall in the number of leukocytes recovery may be expected, while a gradual rise usually forebodes a fatal outcome.

Prophylaxis.—Erysipelas, especially in the newborn, comes under the head of the preventable diseases. If the mother has breast or puerperal infection the greatest care should be taken to prevent the infection of the child. Both direct and indirect contact with cases of erysipelas or of septic infections should be avoided. The child's clothing should be sterilized if it has come in contact with other laundry that has been used about cases of septic infections, and the nurse and those handling the child should be exceedingly careful about the cleanliness of their hands. The child should not be exposed to the exhalations of persons suffering with colds or sore throats.

Treatment.—There is no very satisfactory treatment of the disease and none of the internal remedies formerly in vogue are to be recommended. The tincture of chlorid of iron was formerly thought to be specific, but probably exerts no influence whatever on the course of the disease or its prognosis. Serums have been studied; it has been suggested to use the serum from convalescent or recovered cases.

Kaiser reports the use of injections of 20 c.c. of whole blood which was citrated and injected directly into the muscles. The results were immediate, the temperature dropping to normal. This occurred on the sixth day of the disease when the fall may have occurred independent of the therapy. Roger and Marmarek and others have succeeded in immunizing animals to the Streptococcus pyogenes by increasing inoculations. A bactericidal serum has been made by various laboratory workers and polyvalent serums are at present on the market, but these have not been standardized and they lose some of their value after several months. The results obtained by their use are not uniform and they have not been taken up generally by the profession, although some favorable results have been reported. To be effective the adult dose must be 50 or 100 c.c. preferably administered intravenously. Vaccins have also been suggested and Sill has reported 10 cases occurring in infants with only one death. He used large doses, 80 to 120 million, given at 24 hour intervals. Erdman, however, in a study of 800 cases of erysipelas, 95 of which were treated with autogenous vaccins, came to the conclusion that the mortality was not lessened and that there was no difference in the complications. Autogenous vaccins might, however, be tried in the prolonged or migrating cases (L. Fisher). Hiss' leukocyte extract has been used by McRae. He had a favorable outcome in a case following a mastoid in which injections of 10 c.c. were used, two injections being given on the first day and one injection daily for the succeeding three days.

External applications of all sorts have been suggested. Hippocrates suggested the use of cold water, perhaps as good an application as can be used. Milliken suggests that one of the most satisfactory methods of treatment is to powder the entire region attacked with the disease with powdered stearate of zinc, which is re-applied as it falls or is brushed off. In cases where there is any open wound it is treated just as it would be in the absence of erysipelas. When the face is attacked the same method is used and, if necessary, the eyes are kept moistened with small compresses renewed from a basin of boric acid, and a drop or two of 5 per cent. argyrol dropped into the eyes every few hours, according to the needs of the case. In cases where the leg is infected, if periphlebitis or cellulitis develops, an incision is made as soon as the lesion appears and wet dressings of magnesium sulphate or dilute alcohol applied.

Choksy claims to have obtained favorable results by using saturated solution of magnesium sulphate applied on gauze, wetting the gauze anew every two hours. Arnold suggested the use of buttermilk. Judd collected 1000 cases, adults and children, treated by painting the entire affected surface and ½ in. of the healthy skin beyond with 95 per cent. phenol and waiting till there was a whitening of the skin when the whole is washed off with alcohol. He has seen no evil effects although occasionally the urine has been dark. The temperature usually drops and stimulants may be needed, but the results, he thought, were better than with other methods of treatment. Unfortunately, in children there were more failures than in the adults, 20 per cent. not responding to this method.

Other applications, ichthyol, either in glycerin or in ointments, lead water, bichlorid solutions, picric acid, and iodin have been used. The last named should not be used in young infants. Scècsy recommends a mixture of 10 per cent. each of guaiacol and tincture of iodin in glycerin. Rittler has used hot air, applying it by the use of Bier's cabinet or the Quincke sweat bed, and Jochmann and Schöne have suggested the use of Bier's hyperemia. The multitude of suggestions for local treatment indicates their probable uselessness. The impervious applications and ointments should not be used over too large an area.

The general treatment is important; the child should be in a room which is well aired and every effort should be made to supply sufficient amount of nourishment, which may be difficult owing to the anorexia. Cold sponges or baths may be used for the fever and Kerley advises the use of from 5 to 15 drops of whisky well diluted every two hours in children under two. He states that this is the one condition in which he advises its early use in all cases. Stimulants along general lines may be employed. Epinephrin solutions hypodermically in acute collapse, camphorated oil given the same way where rapidity of action is not so urgent, and digitalis in cases of irregularity of heart action.

Alquier has suggested the use of ultra violet radiation, commencing with 10 minutes and increasing daily up to 15 minutes, the distance from the quartz lamp being from 170 to 100 cm. For older children 15 minutes usually suffices.

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CHAPTER CLIII

MUMPS

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Synonyms.—Parotitis epidemica. Latin: Cynanche parotida. French: Les oreillons. German: Ziegenpeter, bauerwetzel.

Definition.—Mumps or infectious or epidemic parotitis is a specific infectious disease characterized by fever and by swelling and tenderness of the salivary glands, usually of the parotids, but sometimes of the submaxillary and sublingual glands. Swelling of the testicle may also occur and other organs occasionally may be involved.

History.—The history of mumps dates back to Hippocrates, who observed an epidemic on the Island of Thasos and noted that the swelling of the testicle may occur in the course of the disease. His description (Hippocrates, "Epidemics," Book 1, Section 1, Case 1) is so remarkable that it must needs be quoted:

"Ardent fevers occurred in a few instances, and these very mild, being rarely attended with hemorrhage, and never proving fatal. Swellings appeared about the ears, in many on either side, and in the greatest number on both sides, being unaccompanied by fever so as not to confine the patient to bed; in all cases they disappeared without giving trouble, neither did any of them come to suppuration, as is common in swellings from other causes. They were of a lax, large, diffuse character, without inflammation or pain, and they went away without any critical sign. They seized children, adults, and mostly those who were engaged in the exercises of the palestra and gymnasium, but seldom attacked women. Many had dry coughs without expectoration, and accompanied with hoarseness of voice. In some instances earlier, and in others later, inflammations with pain seized sometimes one of the testicles, and sometimes both; some of these were accompanied with fever and some not; the greater part were attended with much suffering. In other respects they were free of disease, so as not to require medical assistance."

It is interesting to note the Greek attitude in regard to infection. Dr. Fielding H. Garrison has called my attention to the fact that Sudhoff maintains that the Greeks were blind to contagion as a fact and saw it only as a theory, since they made no attempt to prevent infectious disease as the Hebrews did and the people who followed them in the middle ages, but the very title of the treatise of Hippocrates ("Epidemic Diseases") shows that he saw clearly that certain diseases occurred en masse, even though he apparently did not understand how they may be communicated from one person to another.

The idea of contagion came through Rhazes from the Orient, and Sudhoff has pointed out that the leprosoria were true isolation hospitals in the middle ages and that after the introduction of the inunction cure of syphilis hospitals became places for the treatment of disease for the first time and ceased to be mere prebendaries.

The other Greek and Roman medical writers and the medieval physicians, as well as those of modern times, have been well acquainted with mumps and its epidemic character. Hirsch has given a partial list of some of the earlier epidemics. The disease is diffused over the entire globe, from the coldest regions to the very hottest. He also points out the numerous epidemics among the military and aboard ships. During the Civil War in this country there were during the first year 11,216 cases in the Confederate Army, and in the second year 13,429.

Distribution and Epidemics.—Mumps has been found in every part of the world, in Europe, America, Asia, Africa, and Australia. Not only has the disease been noted in these various countries, but epidemics have been reported from all of them and it is said that very large epidemics have occurred in India. Ordinarily the epidemics progress slowly and with less severe cases, new cases appearing from time to time. From about one-quarter to one-third of those exposed to the disease take it, but this varies in different epidemics and also with the age of the persons exposed. Barthez and Sanné noted in a boys' school of 540, that after exposure 230 were taken with the disease. In barracks and institutions an epidemic may frequently be confined to one building or one enclosure, and in army camps the disease, which is not infrequent, can generally be easily controlled by group isolation.

Hirsch points out that epidemics of mumps are not infrequent along with the acute exanthema, particularly often with measles, but he does not believe that there is any genetic connection between mumps and the exanthema. Epidemics may last a few weeks or months or sometimes a half a year or more. As a rule, there is an intermission of several years between widespread epidemics, but they may recur every year and may be noticed in one town or village or in a group of villages. Epidemics are particularly frequent in orphanages, barracks, prisons and other places where large numbers of young people are crowded together. The epidemics in such cases may, at times, be limited to one particular group of individuals, particularly if they are kept to themselves. In army camps the disease is not infrequent, but with the modern conception of infectious diseases the spread is usually easily limited by restricting the movements of the group of men in which the disease has appeared.

The season of the year in which the epidemics are most likely to occur is of interest. Hirsch, in 150 epidemics, gives the following figures:

Winter	48
Winter and spring	17
Spring	41
Spring and summer	2
Summer	15
Summer and autumn	4
Autumn	16
Autumn and winter	7

It will be noted that in the 150 epidemics 129 occurred in the cold months. There is no difference in the soil, climate, or race.

The Disease in Animals.—There is an impression, perhaps well founded, that domestic animals may occasionally suffer from the disease by natural means of infection. This, however, is certainly of very rare occurrence and there are few references in the literature. Poore, however, relates an instance in which a dog developed parotitis and orchitis 14 days after his master, who was 17 years old, had the disease. Wollstein found cats most satisfactory for experimental purposes.

The Contagion.—The disease is generally transmitted by direct contact and this possibly from the onset and for some time after. The exact length of time that the patient remains a danger to others has never been definitely determined, but is generally placed at three weeks. Sharpe relates two cases where the individuals were a source of infection for as long as six weeks after the onset of the disease. Indirect transmission has been doubted, but under certain conditions perhaps may occur. It is exceedingly difficult to get instances in which the source of infection can be definitely traced. The disease may also, probably rarely, be transmitted by fomites, as Roth relates a case which was apparently acquired by sleeping in a bed previously occupied by a patient suffering with mumps.

Immunity.—One attack confers an immunity which apparently lasts throughout the life of the individual. There have not been many reports made upon the subject of second and third attacks and Feiling states that he has found great difficulty in proving any cases of second infection. Barthez and Sanné, however, report 30 recurrences out of 230 patients and three of these individuals suffered with a third attack.

Bacteriology.—The studies on the bacteriology of mumps may be divided into two distinct classes, the first dealing with the earlier work, which were attempts to isolate ordinary nonfilterable bacteria; the second group of investigators dealt with studies made upon the theory that the disease is due to a filterable virus. Among the earlier searches for the cause of the disease are those of Capitan and Charrin in 1881. They described a spherical and rod-shaped microbe in the saliva, which they relate is abundant at the height of the disease and disappears on its subsidence. The observation was confirmed by the observations of Boinet. He isolated the organism from the blood and injected the cultures into the tunica vaginalis of a rabbit, which set up an acute inflammation of the testes which resulted in the death of the rabbit in 15 days.

The earlier investigators, almost without exception, described a diplococcus. Among the early observations is the report by Laveran and Catrin in 1893. They isolated a Gram-negative organism in 67 out of 92 cases where the parotids were involved and in 12 out of 16 cases of orchitis. They obtained the material for culture by aspiration. Their efforts to reproduce the disease in animals by inoculation were all failures. Following this a number of different observers reported similar results. Mecray and Walsh, in 1896, and Michaelis and Bien, in 1897, described the same or similar organisms in material taken from Stenson's duct. Busquet and Ferri, in 1896, described a diplococcus which they were able to grow from the blood of 20 consecutive cases. In 1904, Fichera made a careful study of the bacteriology of the disease and all his culture results were negative. He studied all the various tissues and came to the conclusion that the previous observers were dealing with the staphylococcus epidermis albus. In 1906, Tessier and Esmein made another study and succeeded in isolating a Gram-positive diplococcus from the blood of 37 out of 45 cases and in the saliva from Stenson's duct in two out of 10 cases. This organism differed from the one described by Laveran and Catrin in that it was Gram-positive. Animals inoculated with cultures died from a fatal septicemia. In 1909, Herb isolated a diplococcus from the lung, testes, cerebrospinal fluid, bile, and the parotid gland, and inoculations with the cultures gave rise to an acute interstitial inflammation of the testes without suppuration and to a parotitis in monkeys and dogs. Herb's material, however, was derived from a man who had died from a disease resembling mumps, but a suppurating parotitis was found at autopsy which, of course, makes it extremely doubtful whether the disease was mumps or not.

The more recent studies have started at the subject from a new angle. In 1908, Granata suggested that the virus might be filterable and obtained the saliva from two patients, passed it through a filter and inoculated it into rabbits, injecting some into the blood, some into the parotid glands, and some subcutaneously. A rise of temperature lasting three days followed the intravenous injections, and the other inoculations were followed by a swelling of the parotid glands which lasted one to two weeks. A couple of years ago, Gordon used a filtrate for the intracerebral inoculation of monkeys. He was able to produce a fatal meningitis, a marked increase in the leukocytes and also marked degeneration in the neurons of the cerebral cortex, and the anterior horns of the cord. Cultures from the meninges were sterile. One animal, inoculated intraperitoneally and intravenously, was taken in the eleventh day with swelling of the parotid and stiffness of the jaws. This animal recovered. The disease could not be transferred from one animal to another by using filtrates of the cord from the fatal case. Nicolle and Conseil injected the fluid aspirated from the parotid gland of children ill with mumps into the parotid gland of three monkeys. The animals developed fever lasting two to seven days, and in one of the monkeys the parotid was swollen. No bacteria could be demonstrated in the fluid used in the injection. The animals showed a mononuclearcytosis in one instance.

Wollstein has made a thorough study, using cats, rabbits, and monkeys, but most of the work was with cats, inasmuch as the rabbits and monkeys did not show very promising results. The material for the injection was obtained by having the patients with swollen parotids rinse the mouth with sterile salt solution and expectorate into a sterile glass dish. In some instances the parotid was gently massaged at the same time. This material was filtered through a new Berkefeld filter and the filtrate was found to be uniformly sterile, both by aerobic and anaërobic methods. This filtrate was used to inoculate the cats, injections being made into the parotid gland and into the testicle. The animals recovered rapidly from the anesthetic and showed no ill effects from the inoculation. On the following day the temperature rose, usually 0.5°C., but there was no increase in the leukocytes. There was usually a slight tenderness about the inoculation which was evidently of mechanical, and not of inflammatory, origin; this always disappeared after 24 hours, so that the animals were apparently well on the second day, although there was this slight increase in their temperature noted above. After six or seven days there was tenderness and swelling in the parotid or in the testes. Two days after the inoculation the leukocytes began to increase and reached the maximum in 7 to 14 days, coinciding with the height of the fever. The swelling in the parotid lasted two to five days while the testicular swelling usually lasted from 10 to 14 days. All the symptoms began to disappear in the third week, the leukocytes reaching normal first, the tenderness disappearing at the same time while the fever persisted for another week. The appetite was only slightly affected and at no time did the cats seem particularly ill. The changes in the blood which began on the second day consisted of first, a polymorphonuclear leukocytosis which precedes the glandular swelling. This initial rise is followed by a decline, and subsequently there is an increase in the small lymphocytes of from 7 to 10 per cent. This blood picture is very similar to that observed in mumps in man with testicular complications.

Aubertin and Chabanier have observed an initial rise in the polymorphonuclear leukocytosis in all human cases which they examined and subsequently there was an increase in the lymphocytes. Wile noted that when the testicle became involved there was a change from lymphocytosis to polymorphonuclear leukocytosis.

The disease so produced could be transmitted from cat to cat by using extracts or emulsions of the organs. The best time for reinoculation was from the fourteenth to the seventeenth day when the testicular swelling, the leukocytosis and the fever were highest. Transfers made during the first 7 to 10 days were less uniform and successful. Control observations were made with normal organs and it was found that intraparotid and intratesticular injections of extracts of normal parotid gland and testicle may cause a slight rise of temperature and a leukocytosis limited to the polymorphonuclears. The swelling and tenderness are absent and there is no lymphocytosis. Other control observations made with filtrates of normal saliva injected into the parotid and testicle cause a very brief rise of temperature, but there was no change in the leukocytosis, no swelling and no tenderness. The histologic changes in the parotid gland consist chiefly of edema of the interlobular tissue with mononuclear infiltration above the ducts and elsewhere. From cases that lasted some time the ducts were sometimes dilated. In some instances glands which were congested and edematous to the naked eye showed but little change under the microscope. The changes in the testicle were of two kinds. Constant changes consisted of degeneration of the epithelium and interference with spermatogenesis. The inconstant changes consisted of an infiltration of cells between the tubules and a swelling, or even a multiplication of the interstitial cells. The changes were very much intensified by successive transfers through a small series of cats.

Another interesting observation was made with the blood serum of cats that had recovered from a previous inoculation. When the extract or emulsion used for inoculation was mixed with serum from such animals the pathological changes were either prevented altogether or greatly reduced. The serum from normal cats, on the other hand, had no such inhibiting effect.

The observations made by Wollstein prove quite conclusively that the saliva from mumps contains a filterable virus capable of producing very definite pathological changes when inoculated into the testicle and parotid gland of cats. What the nature of this virus is and its exact relation to epidemic parotitis will have to be determined by further observations. This is, however, the most enlightening piece of work that has been done on this subject.

Pathology.—The disease as it occurs in man has not been studied very many times so that any valuable opportunities to secure pathological material should not be allowed to pass. Virchow described the disease as an inflammatory serous and cellular infiltration of the intra-acinous and peri-acinous tubules. In view of the paucity of our information of the changes in the gland in the human being the changes noted by Wollstein in her "Experimental Study of Parotitis" (mumps) may be cited. The gross appearance of the parotid gland consisted of its being larger in size and of a deeper pink color than normal. The inoculated gland was more moist than the uninoculated and showed on section a gray cloudy appearance due to swelling of the acini. No other changes occurred. The adjacent lymph-nodes were usually congested, but not definitely enlarged. The histologic changes were not constant for all the transfers of every strain; the most marked changes appeared coincidently with the third and fourth transfers. In some glands there was infiltration of the interlobular tissue with mononuclears and a few polynuclears in addition. The infiltration was most intense about the secretory ducts, which were sometimes dilated, and in these instances the epithelium of the acini was swollen and clouded. The areas of cellular infiltration were more pronounced in some parts of the glands than in others. The gross appearance of the testicle was the increased size, but was different in color, but the cut surface was more gray, cloudy and moist. The histologic changes were more constant than those in the parotid and were more pronounced in the epithelium than in the separating frame work of the gland. Epithelial changes in most part were present in practically all of the inoculated parts of the testes. Fibrous tissues with some decrease in the size and numbers were found in the atrophic testes.

Symptoms.—Incubation Period.—There is considerable difference of opinion regarding the incubation period, but all observers agree that the period is rather long and the report of the Clinical Society of London, in 1892, places the average incubation period at 21 days with variations of from 12 to 25 days. The various observers who have studied the disease give slightly different figures. Dukes, for example, believes that the average is 17 days with variations at 16 to 23 days. Roth places the average at 18 days, with variations between 4 and 25. Manine, after observations in the French navy, places the limits between 5 and 19 days. In four cases in which Feiling believed he could place the incubation period accurately two developed in 22 days, one in 17 days and one in 19 days. There have been a number of reports dealing with longer incubation periods, Bloomfield, for example, reporting a case with an incubation period of 26 days, Penny 27 days, Douglas 29 days and 35 days, and Bernutz one case apparently developing after six weeks. In these longer periods it must be always borne in mind that it is a possibility of the individual having had a second exposure.

Onset.—Prodromes may or may not be present. If the history is carefully taken they will probably be noted in about one-third of the cases and some observers have attributed symptoms as early as eight days before the involvement of the parotid along with the prodromes, but ordinarily whatever is noted occurs from 12 hours to two days before the swelling of the gland, although not infrequently there is some indisposition or even severe symptoms for four days before the swelling. The prodromes may be wanting and the swelling of the parotid or other glands may be the first thing noted. The disease usually begins with a fever, which may or may not be accompanied with a chill, and there is the general malaise which practically always attends rise in temperature. Vomiting or diarrhea may be noted occasionally and a not uncommon symptom and one which often causes the patient considerable alarm is vertigo. In children nose-bleed is not infrequent. In some patients there may be sweats and fainting spells have been reported, or the first thing noted may be pain in the ear. Occasionally trismus may be present and may give rise to the thought that there is a beginning tetanus. The disease may come on with symptoms which might not lead one to think of mumps at first. In place of the swelling of the parotids or other salivary glands the orchitis may be the first thing noted or there may be severe nervous symptoms, either symptoms of meningeal irritation or coma.

Fever.—This may precede the swelling or it may come on with it. In some cases there may be very little or no fever throughout the entire attack, usually, however, the temperature ranges from 101 to 103 or even higher. It may come on a day or two before the swelling of the gland and generally disappears as the swelling subsides, or many times several days before. Following an attack of mumps it is not uncommon to note a subnormal temperature for a number of days after the temperature has been elevated.

Pain.—There is great variation in the amount of discomfort which patients suffer, some do not complain at all, but there is usually some discomfort and in some individuals, particularly in those of nervous temperament, the suffering may be extreme. The pain is increased on pressure and the glands involved are always tender whether pain is present or not. The pain is also made worse by mastication and salivation, for example, the taking of acids or highly spiced foods may cause twinges of pain, and in many individuals the mere mention or sight of lemons or pickles or vinegar may do the same thing.

Swelling of the Glands.—This usually involves the parotids. It may be on one or both sides, more frequently noted on the left than on the right. Sometimes the disease starts in both glands at the same time. Where it starts in one it usually involves the other in from one to four days, but both glands subside simultaneously. The swelling generally increases very rapidly and varies in different individuals in its extent. It usually lasts from three to six days, remains stationary for a day or two and then subsides gradually so that the gland may apparently be normal at the end of one week. It is usually 10 days or two weeks before the subsidence is complete and in severe or exceptional cases the gland may be swollen for over three weeks and it may be even a month before there is an entire disappearance of the enlargement. In very exceptional instances the enlargement may persist and Thomson has observed a case in which the swelling lasted for seven years.

At the onset the swelling is boggy, later it becomes tense and firm; there is occasionally a little redness, particularly just back of the ear; sometime the redness may be so marked as to suggest an erysipelas. In occasional cases the swelling and edema may be so marked as to disfigure the patient beyond recognition, the general appearance suggesting some ludicrous imitation of a human face.

It should be borne in mind that when the parotid is involved the swelling is directly under the ear and the small fossa just below the ear and just behind the angle of the jaw, which one can usually place the finger upon, is obliterated. This point is of great value in the diagnosis between swellings of the parotid and involvement of the adjacent lymph-nodes. Next in frequency the submaxillary glands are involved and occasionally the sublinguals, as noted by Henoch. These glands may be involved at the same time as the parotid or may come on before the parotids are involved, or in some instances they may be the only glands showing any change.

Throat.—The throat, in many cases, shows no changes whatever, but in the severer ones there may be an edema and considerable difficulty in swallowing. The tonsils may be pushed inward and if large this may render swallowing very difficult, especially if the disease is bilateral and more so if there is much edema present. Various authors have described an enanthem, but this certainly can be nothing more than a complicating stomatitis.

Saliva.—The saliva may be normal in quantity, it may be nearly or entirely absent or it may be excessive in quantity. Sicard and Dopter made a study of the saliva taken from Stenson's duct. In normal saliva there is an entire freedom from cellular elements, but in mumps cells are found, at first lymphocytes, large mononuclears and polynuclears and later the glandular desquamation and liberation of casts. As the swelling subsides the cellular elements disappear and the saliva returns to normal.

The amount of saliva varies in different cases; in some it is normal, in others it is very much diminished or even entirely suppressed, which leads to a dry mouth which is generally complained of bitterly by the patient, while at other times there is a tendency for the saliva to collect in the mouth, either owing to the increase or due to painful swallowing.

Orchitis.—This is the most common complication or incident in mumps and, as mentioned before, in some instances the involvement of the testicle may be the only lesion or may precede involvement of the other glands. It varies somewhat in different epidemics and in the experience of different observers, but bears a pretty constant ratio to the age of the patients. Catrin states that it occurs in 16 per cent. of all males, regardless of age. Dukes, in 23 cases, had an instance of 37.5 per cent. and in another small epidemic of 30 cases, in 20 per cent. There is a general impression founded on pretty good evidence that the involvement is less frequent when the patients are kept at rest in bed than if they are about, and yet Dukes, in the epidemic just referred to of 30 cases, had the 20 per cent. involvement in spite of all the patients being in bed at least eight days.

Involvement is most common about puberty and in young adults. It may come on as the first sign of the disease, but ordinarily makes its appearance some time between the third and eighth day after the involvement of the parotids. Dukes gives the seventh as the day on which the involvement is most likely to occur, while Chauvin states that it may occur any time between the third and eighteenth day after the onset. There is a difference of opinion whether the epididymis is involved first or the reverse, or whether they both occur simultaneously. This difference of opinion is doubtless due to whether all three things may be met with. Trousseau has described a case in which the swelling was particularly of the epididymis. Chauvin, in a small series of cases, found that there was involvement of both epididymis and testicle in 15, of the testicle alone in three, of the epididymis alone in two. He also describes three cases in which the vas deferens was involved alone.

The swelling lasts, as a rule, from three to five days and then gradually subsides. It is accompanied with the usual signs and symptoms of orchitis with marked swelling and tenderness of the gland; the patient usually suffers a great deal of pain and has a high fever. As a rule, involvement is one-sided, but both glands may be involved either simultaneously or separately. Following the involvement atrophy of the testicle is very frequent. In some instances this takes place very rapidly and Lebouillet describes a case in which it was pretty complete in three weeks' time. In other instances the atrophy takes place more slowly and may be more or less complete at the end of six weeks.

Pancreatitis.—That the pancreas might be involved in mumps was suggested by the early writers, but the chief interest in it dates from 1897 when Cuche described tenderness over the pancreas in 20 out of 26 cases. The symptoms were those of an acute pancreatitis, usually sudden in onset with severe and incessant vomiting, which may be severe enough to cause hematemesis. There is tenderness over the epigastric region and in some instances an elongated tumor in this region has been noted. There is undigested fat in the stools and sometimes blood. The pain may not be limited to the epigastric region, but may be located anywhere between the xyphoid cartilage and umbilicus and may radiate along the costal arches and may extend to the interscapular region or to the dorsal or lumbar regions. In about one-half of the cases there is diarrhea.

Severe cases are certainly very rare. Simonin noted 10 in 652 cases, and Raymond four in 60. The disease comes on between the first and twelfth days, as a rule, but the predilection is for the third to sixth days and ordinarily lasts from two to seven days when recovery takes place. Death, however, may take place and there is a record of one autopsy, reported by Lemoine and Lepasset in 1905. In this instance the patient had an ordinary mumps with orchitis and on the fourteenth day was taken with vomiting, then jaundice of a very severe type and death ensued four days after the onset from a profuse hematemesis. The autopsy showed that the jaundice was caused by the swollen pancreas pressing on the common bile duct. There was swelling and edema of the pancreas and the epithelial cells were found swollen and degenerated, and there was compression of the islands of Langerhans.

In one case Cammidge examined the urine and stated that it gave a pancreatic reaction and there were present oxalic acid crystals, acetone and diacetic acid. In this connection it is interesting to note that as far as one may judge from the reports that glycosuria is rare in mumps, although Barbieri has reported an instance coming on on the seventh day in a child six years of age. There was acute abdominal pain, vomiting and diarrhea and a polyuria and glycosuria that lasted for 15 days. In this case fat was also found in the stools.

Nephritis.—Involvement of the kidney has been noted by a great many different observers. This complication seems to be more common in males and Miller has collected 30 cases. This complication is more frequent than the reports would seem to indicate, inasmuch as but few of the cases find their way into the medical literature. The symptoms usually come on early in convalescence, but the onset may be delayed for four or five weeks. There is nothing strikingly different from the nephritis in the course of or following any acute infectious disease. There is albuminuria, and sometimes hematuria and edema and uremia and the other well known signs and symptoms of nephritis may be present. As a rule, the disease lasts but a short time, usually a week or two and then generally subsides. Occasionally, it may run into a chronic nephritis and death sometimes results. Sylvester reported a very interesting case in which after a severe onset with swelling of the parotids the swelling disappeared after 24 hours and there was a swelling and tenderness of the kidneys together with cessation of renal function. There were marked cerebral symptoms, all of which passed off followed by a complicating orchitis on the eighth day.

Blood.—The earliest observations on the blood did not show much, but in 1902, Sacquépée showed that in cases without orchitis there was a slight leukocytosis with a relative increase of the mononuclear cells. He believed that when orchitis was present that it caused an increase in the polymorphonuclears. Krestnikow made similar observations and Pick likewise, but Pick believed that an absence of polymorphonuclear leukocytosis might be of some value in differential diagnosis between the orchitis of mumps and that occurring in gonorrhea. Barach reports a leukopenia in a study of 11 cases and believes that the severer the case the more marked the blood changes. He also noted the relative increase in the lymphocytes.

The two best blood studies are by Wile and Feiling. Their results may be summarized, to quote Feiling, as follows:

1. The blood of mumps shows definite changes in the corpuscular content.
2. That these changes consist (*a*) in a slight increase in the total number of leukocytes, (*b*) in a lymphocytosis, which is both relative and absolute.
3. That this lymphocytosis is present on the first day of the disease and persists for at least 14 days.
4. That the occurrence of orchitis does not invariably alter the blood picture.
5. That changes in the blood are of distinct diagnostic value in differentiating mumps from other inflammatory swellings of the parotid or submaxillary salivary gland.

Wile states that the lymphocytosis persists until all the swelling has disappeared and that it is most marked in children, and he found an increase in the polymorphonuclears with the onset of the orchitis. He also states that there is no secondary anemia.

More recently Aubartin and Chabanier have reported an initial polynuclear leukocytosis in all cases of mumps examined. In cats, Wollstein found that the white blood cells began to increase on the second day following inoculation. The first change was a polymorphonuclear leukocytosis which precedes the glandular swellings. This initial rise is followed by a decline after which the lymphocytes increase. The increase is confined to the small lymphocytes which are increased from 7 to 10 per cent. of their initial number. Nicolle and Conseil, in one of their monkeys which had been inoculated into the parotid, but not into the testicle, found an increase in the mononuclear cells.

The Involvement of the Nervous System.—In 1758, Hamilton recorded a case of death in a man 22 years of age with what was evidently a meningitis with maniacal symptoms, the death occurring on the second day. Among the other early instances areAstley Cooper's case of a child who died on the eighth day, and Malsbrouche and Niemeyer have also discussed involvement of the nervous tissue in some detail. The involvement of the nervous system is not of very uncommon occurrence and probably in most instances of an inflammatory nature, although there is some reason to believe that some of the cases are due to toxemia.

Cerebral and Meningeal Lesions.—These have been described in detail by a number of observers; in 1885 by Lannois and Lemoine, and in 1913 by Acker and others. Gallavardin thought that involvement of the meninges was a precursor of orchitis. There have been very few observations made on the anatomical changes that take place, but Maximowitch had an opportunity of making an autopsy in a case dying of convulsions and found that the surface of the brain was edematous and the sulci filled with a semi-fibrinous exudate. Ordinarily the clinical picture produced is that of meningismus or at times of marked meningitis. The symptoms need not be detailed, but there is headache at the onset and delirium is common throughout the course of the disease and convulsions are not uncommon. Death may ensue or other results may follow, such as hemiplegia or aphasia, as in the case reported by Lannois and Lemoine where there was a right hemiplegia and aphasia coming on one week after mumps, followed by gradual recovery. Tremors and involuntary movements of the choreiform type may follow the cerebral type and Lafforgue has noted a case of paramyoclonus coming on six weeks after recovery. Monro, in 1883, had an instance, a very severe case in which there was orchitis, delirium, hyperpyrexia, followed by unsteadiness of gait, incoördination of speech and agraphia; and Sorel a somewhat similar case with delirium, orchitis, but followed by aphasia which lasted for 15 months, but which finally ended by gradual recovery. Findlay, in 1906, reported a case of infantile hemiplegia coming on a few days after mumps. It is believed that symptoms may be caused by pressure on the jugular, by a diffuse meningeal encephalitis, or by embolism from endocarditis. Roux has summarized the subject as follows:

"1. Meningeal symptoms are frequent, typical meningitis is rare.

"2. This usually occurs at the height of the disease and sometimes before.

"3. There is usually a marked lymphocytosis in the cerebrospinal fluid.

"4. There is usually rapid subsidence of the symptoms."

Sicard has described a case in which the patient had mumps with meningeal symptoms at which time there was marked lymphocytosis of the cerebrospinal fluid. This was followed some weeks afterwards with headache and vertigo and the patient gradually developed hydrocephalus accompanied by a spastic diplegia, intentional tremor, aphasia nystagmus, and scanning speech. The patient, at the time of the report, was 15 years of age and the disease had begun two years before.

Cranial Nerves.—Involvement of the cranial nerves has been reported a number of times. It is supposed by some to be due to the direct compression of the swollen glands; others that it is due to a basal meningitis, and another idea is that it is of toxic origin. Against the direct compression is the fact that facial paralysis is rare in the other diseases in which swelling of the parotid occurs. Cases have been reported by a number of different observers, among whom may be mentioned Dopter, Daireaux, Lacroix, and Hertz. Courand and Petgis, in a study of 60 cases of the disease showed seven cases of facial paralysis. In all cases it was unilateral, came on from three to nine days after the onset and lasted from 6 to 10 days and cleared up entirely. In the case reported by Hertz there was a reaction of degeneration present. In some of the cases it was noted that there was a loss of taste as well. There may be lesions in the peripheral nerves together with meningeal symptoms, for example: Dopter reports a case of herpes of the third division of the fifth nerve together with loss of sensation, which was accompanied with severe headache and vomiting. The cerebrospinal fluid showed a lymphocytosis.

The Spinal Cord.—There have been a few instances in which the spinal cord was involved following mumps, but the condition is certainly an unusual one. Missimilly records what he calls a poliomyelitis occurring in mumps in which there was a complete flaccid paralysis, loss of reflexes, but there was recovery with the exception of the muscles of the left thigh which were atrophied, and the nerves showed a reaction of degeneration. Warrington gives an instance of an ascending myelitis coming on 10 days after the appearance of what was diagnosed as mumps. There was complete flaccid paraplegia, absence of reflexes, incontinence of urine, patulous anus, anesthesia up to the lesion, and death resulted from paralysis of the diaphragm.

Peripheral Neuritis.—There are a number of cases of this on record, among others those reported by Gallavardin, Chavannes, and Ravilliod. Joffroy has recorded an instance of a complete flaccid paralysis of all the extremities coming on on the twentieth day, accompanied with loss of the deep reflexes and dimunition of the cutaneous sensibility, but followed by complete recovery. The cases reported by the other observers are somewhat similar and apparently the outlook in these cases was good for eventual recovery.

Herpetic eruptions have been observed. Sicard gives an instance of supraorbital and auriculo-temporal herpes coming on nine days after a double parotitis. Dopter had a case of double orchitis with a left facial paralysis and paresis of the left half of the palate and dilatation of the left pupil with paralysis of the accommodation on the left side, and the cerebrospinal fluid showed a lymphocytosis.

The Cerebrospinal Fluid.—This has been studied by a number of individuals. In 1902, Monod wrote his inaugural thesis upon this subject and since that time observations have been made by Dopter, Sicard, Chauffard and Boidin, Feiling, and others. Monod described a lymphocytosis, even when there was no evidence of meningitis and this was confirmed by many observers. Chauffard and Boidin made a study of a case in which there was headache, insomnia, and slow pulse (60 to 70) and a very marked lymphocytosis which persisted for 46 days, and a similar case has been reported by Nobecourt and Fearnley. Feiling studied a case and the observations of others and concludes that the lymphocytosis in the cerebrospinal fluid occurs in mumps when that disease is complicated by meningitis or by lesions affecting the cranial nerves; and that a lymphocytosis has been described in mumps in which there were no other lesions of the nervous system.

The Ear.—One of the ear complications is the sudden and often permanent deafness, one of the most distressing of the complications of mumps. There has been considerable discussion as to the cause of this and apparently it is due to labyrinthine disease, but Ménière thought that it might be due to a meningitis, at the base of the brain, and Voss thought it might be caused by a central lesion. The subject has been reviewed by Lannois and in 1898 Gallavardin collected 54 cases and added five of his own. In 1914, Voss made another collection of cases.

As a rule the deafness comes on suddenly, although there may be some premonitory tinnitus and vertigo. It usually occurs between the fourth and fifth day and involvement is usually permanent. Minor studied eight cases in which he found three to have changes in the middle ear only, three in the internal ear only, and in one case the semi-circular canals and cochlea were apparently involved. Hubbard has made a study of this subject and states that in 3 to 5 per cent. of the deaf mutes in the United States mumps is given as the cause. There are about 50,000 deaf mutes in the United States, so that one or two thousand of these resulted through this disease.

Treatment of the condition is exceedingly unsatisfactory, but Hubbard suggests that spinal puncture be tried, even though there be no connection with the endolymph, it may lower the tension in the subarachnoid and may drain the perilymph and thereby reduce intracapsular tension. He also calls attention to the fact that hypoacusis of obscure origin can occasionally be traced to mumps.

The Eye.—Eye symptoms may be occasionally noted, often of a most serious nature. Inflammatory changes are rare, but conjunctivitis, keratitis and ulcerative keratitis, iritis and retinal congestion have all been reported as occurring during the occurrence of mumps. Extraordinary instances of chemosis and edema of the face may be occasionally seen. I have seen one or two instances in which the diagnosis may have been easily overlooked owing to the enormous amount of disfigurement which entirely obscured the involvement of the parotids for a time. Photophobia and lachrymation are not uncommon, but by far the most important fortunately not a common incident, is the occurrence of optic atrophy which may follow an optic neuritis caused by mumps. Antonelli (1903) has collected 18 cases of optic neuritis. In 1883, Talon reported a case which occurred one month after the attack. Woodward, in 1907, reported a case of unusual interest in a girl of 11 who, three weeks after an attack of mumps, was taken with vertigo, lachrymation, and suffusion of the eye which was followed by complete blindness with marked atrophy of the optic nerve. Three and one-half years later the eye was removed for an anterior staphyloma at which time the completeness of the atrophy was demonstrated in the specimen.

Various other eye affections have been occasionally observed. La Roux has noted toxic amblyopia with septic scotoma for green and red which came on 15 days after the onset of the mumps, but disappeared completely after six weeks time. Campari had a case of hemeralopia which lasted for five days and then gradually disappeared. Madonnet has noted paralysis of the accommodation and uvula which disappeared after a few weeks.

Circulatory System.—Following attacks of mumps there may be a slow or intermittent pulse and with this a low temperature and a tendency to syncope. Endocarditis and pericarditis are rare.

Respiratory Tract.—All sorts of inflammatory conditions of the respiratory tract may complicate mumps by occurring coincidentally. These are added infections and bear no particular relation to the mumps infection. Coryza, bronchitis, congestion of the lungs and lobar or bronchopneumonia may all be observed. Edema of the glottis is a very infrequent, but very dangerous complication.

Metastasis.—Other structures of the body may be involved, most frequently the testicle in the male and in the female the breasts, ovaries, and labia majora. Involvement of the female generative organs are not as common as those in the male, although cases of undoubted involvement of the ovaries and breasts have been reported. The swelling of the inguinal lymph-nodes may occur in both sexes and at times other lymph-nodes may be enlarged and tender.

Complications.—There have been a great many different complications reported as following mumps. Perhaps apart from those described above a good many of these are only coincidences, but pain or swelling of the joints or bursæ has been noted sufficiently often to lead one to conclude that it is sometimes part of the disease process.

Edema of the chest wall has also been described and Simonin has reported an instance of acute swelling of the thyroid with tachycardia and tremor, but which ended in complete recovery; and Solomon has reported four case of phlebitis occurring in the same family in the same epidemic.

Complications are numerous and vary greatly in different epidemics. In one epidemic one particular complication may be quite frequent, that is, epistaxis, while in other epidemics some other special complaint frequently may be met with, as abdominal pain or diarrhea.

Unusual Abdominal Mumps.—Chillingworth gives an instance of a female, aged 22, taken suddenly with acute abdominal pain and vomiting. The pain continued for two days after the onset, was most marked about 2 in. above the umbilicus, but the abdomen was rigid and flat. The temperature was 102 and pulse 100. Later on there was pain over the ovarian region and on the twelfth day both parotids were involved and ran the usual course.

Diagnosis.—This is, as a rule, easy. The history of exposure, with large swelling the center of which is the tip at the lobe of the ear, usually suffices. The most frequent cause of error is enlarged lymph-nodes or pharyngeal abscesses. The former are usually somewhat lower down so that the finger may be placed in the fossæ just behind the angle of the jaw, which cannot be done in the swelling of mumps and there is usually, although not always, a definite cause for the adenitis, either some involvement of the throat or carious teeth and suppuration is quite frequent. Most of the non-specific cases of parotitis are more chronic in their nature and suppuration is not infrequent, especially if it occurs in the course of a pyemia. These other forms of mumps may be classified as follows:

(*a*) Following or during infectious diseases. Typhus fever, typhoid, pneumonia, scarlet fever, and diphtheria, may be especially mentioned; but swelling of the gland may occur in any infectious disease and suppuration is very common. It is not very rare with syphilis. In parotitis due to the pneumococcus or to pus-producing organisms the pus may usually be squeezed out of Stenson's duct.

(*b*) From septic infections, most commonly after pelvic or peritoneal inflammations, appendicitis, cystitis, and pyelonephritis. In these cases the affection may be sympathetic or due to infection.

(*c*) Following disease or injury of the abdominal or pelvic organs, and rarely from operations upon other parts of the body. The submaxillary and sublingual glands may also be affected. Bucknall gives the following list of operations which have been followed by parotitis, even though the operation was entirely aseptic: Exploratory laparotomy, gastrotomy, and other operations upon the stomach; enterectomy, colotomy; hernia operations; ovariotomy; operations upon the uterus and tubes; renal operations; operations on the liver and gall-bladder. To this list may be added castration, or operations on or injuries of the testes, the insertion of a pessary, the passage of a catheter, excision of hemorrhoids, and amputation of the leg. Delivery, abortion, menopause, or disorders of menstruation may be followed by parotitis.

(*d*) In chronic diseases, as diabetes, and any grave form of asthenia, and in the general paralysis of the insane. Symmes has called attention to chronic bilateral occurring in the insane, and reports five cases, all over thirty years of age. Three of these patients had syphilis.

(*e*) In chronic poisoning, as that due to mercury, lead, or the iodids.

(*f*) In association with facial paralysis, as in the case reported by Gowers.

(*g*) In Mikulicz's disease, in which there is enlargement of the salivary and lachrymal glands, coming on without any apparent cause.

(*h*) In gaseous tumors of Stenson's duct, such as are seen in glass-blowers and musicians.

Primary Purulent Parotitis.—Bretschneider has made an interesting study of this subject. He found most cases occurring in the first few days or weeks of life and were either in premature children (31 per cent.) or in children previously poorly nourished. The affection is accompanied with high fever, marked swelling of the parotid, and the chief diagnostic feature for mumps is the fact that in almost all cases pus may be pressed out of Stenson's duct by pressure on the gland. In some instances the mouth of the duct was enlarged and reddened and showed a purulent discharge. The mortality was 69 per cent.

An article of interest on "Secondary Parotitis" has been written by Maggs.

Prognosis.—This is, as a rule, good. The disease itself is limited and always comes to an end. The chief dangers are the possibility of a deafness following labrynthine disease, or blindness from optic atrophy, or atrophy, or lack of development of the testicle following orchitis. This is usually only upon one side, but may, in some instances, be bilateral. In these latter cases the virility is usually retained. Stewart has reported a death from syncope on the fifth day, previous to which the breathing had been asthmatic. Suppuration rarely occurs, never in uncomplicated mumps. The cases in which suppuration and gangrene have been reported either are not mumps or are due to accidental infections.

Treatment.—The course of mumps is not influenced by any treatment known at the present time, but much can be done to make the patient more comfortable and to relieve pain. Food should be liquid or soft so that it may be easily swallowed without mastication, and acids and highly seasoned foods should be avoided. A mouth wash should be used to keep the mouth clean as brushing the teeth may be impossible. The external application of heat is grateful to many patients while others find that the ice bag is more effective in relieving pain. The skin is usually stretched and tense and applications of various kinds have been recommended, usually simple ointments or glycerin mixtures are used and various medicaments are often mixed with these. Five per cent. guaiacol in ointment or in glycerin may be used while belladonna ointment has been highly recommended, and methyl salicylate applied over the gland two or three times a day may help to relieve the pain. Internally a dose of calomel or a saline should be given at the onset and the bowels kept open during the attack. Anodynes may be given if necessary. Codein with or without sodium bromide or antipyrin will be found most satisfactory. Tonics, especially iron, may be used during convalescence.

Protective Therapy.—In a number of infectious diseases attempts have been made to use the blood from convalescent or recovered patients, either as an agent in combating the disease or in preventing it. Poliomyelitis, cerebrospinal fever and scarlet fever have been made the subject of observations along this line. Hess has made a report on some studies in the immunity of mumps in the Hebrew Infant Asylum in New York. During the winter of 1912–1913 there was an epidemic of mumps in the institution which included 100 cases. During the winter of 1914–1915 there was a similar epidemic of 80 cases. None of the children who had the disease in the first epidemic were affected in the second, and an attempt was made to immunize children with the blood of convalescent patients. Many of the children in the asylum had more or less complete histories as to previous diseases, and 20 who had not had mumps were selected. These were inoculated with the blood of children convalescing from the disease, using 6 or 8 c.c. of the blood drawn from the vein at the elbow of the donor and injecting it intramuscularly. These children were divided into three groups. Those of the first group were inoculated with blood of the patients who had just recovered and in whom was still some swelling of the parotid. A second group was inoculated with blood from patients about 10 days recovered from the disease, and the third group from children who had had the disease several years previous. The injections were made when the epidemic had reached a considerable height and all of the children inoculated were exposed to the disease. Not one of the inoculated children contracted it, although other children in the same ward did. There were no local or constitutional reactions. Care was taken to avoid syphilis, and presumably tests were made to determine whether hemolysis would occur, although this is not stated.

Surgical Treatment.—George G. Smith has performed an operation suggested by Hugh Cabot on the theory that the atrophy of the testicle results from the increased intratesticular pressure caused by the inflammation and that if this tension was removed by splitting the tunica albuginia, the circulation would be restored and the testicle preserved. Smith operated on two cases, one aged 22 and one 27 years. The operation consisted of a 21 in. vertical incision along the anterior aspect of the left side of the scrotum and then the tunica vaginalis was opened, allowing about 1 oz. of turbid yellow fluid to escape. The testicle was about three times its normal size, and there were numerous small, punctate hemorrhages. The epididymis was very dark red and intensely congested. About a dozen small incisions were made parallel to the long axis of the testicle and extending through the tunica. About six openings were made over the epididymis. A rubber drain was inserted and the scrotum tightly compressed in an Alexander bandage. The drain was removed three days later and the patient left the hospital two days after that. At this time the testes were the same size.

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CHAPTER CLIV

SCARLET FEVER

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Chicago, Ill.

Definition.—Scarlet fever is an acute contagious disease, characterized by sore throat and a scarlet cutaneous eruption.

Historical.—In ancient medical literature there is no clear description of a disease which can be certainly recognized as scarlet fever. During the seventeenth, eighteenth, and nineteenth centuries the various epidemic diseases were gradually differentiated. This was always rendered difficult by the frequent simultaneous occurrence of two or more diseases in epidemic form, and the occurrence of mild and severe forms of a disease often led even acute observers to erroneously conclude that two or more distinct diseases were being dealt with instead of one. What we now recognize as scarlet fever was long considered as two distinct diseases, and it was much confused with both measles and diphtheria.

Scarlet fever seems to have become epidemic in Spain about 1610 and from there to have spread to Italy. Several fairly exact descriptions of the disease were written by Spanish and Italian writers of the time. In Saxony Sennertus[106] about 1625 gave a very good description of severe scarlet fever, including the eruption, scaling, angina, delirium, arthritis, and dropsy. In 1664 Schultzius[105] described the same disease as it appeared in Poland. Among the earlier English authors there was at first a disposition to confuse scarlet fever and measles, and the milder and more severe forms of scarlet fever were not at first recognized as types of one disease. Sydenham[111] in 1676 was the first to apply the name "scarlet fever" to the disease. He described a very mild type of which he says: "This ailment—we can hardly call it more—is dispelled without either trouble or danger." He failed to note angina or dropsy. Similar mild cases were later described by Sibbald,[107] Dover,[27] and DeGorter.[21] It is not impossible that Sydenham observed rubella and named it scarlet fever, but, at least, he is responsible for the name which has been continuously used every since. Morton[81] in 1694 described scarlet fever, but he confused it with malignant measles to which he thought it related.

In 1736, Wm. Douglass[26] of Boston wrote "The practical history of a new epidemical eruptive miliary fever with an Angina Ulcusculosa which prevailed in Boston, New England, in the years 1735 and 1736." Doctor Douglass was born in Scotland in 1695 and settled in Boston in 1720, where he died in 1752[118b]. He was a man of excellent education. He took an active part in the controversies regarding variolous inoculations of the time and was an ardent botanist. His treatise on scarlet fever stands as the first real contribution of America to the medical literature of the world.[3] He was the first English writer who gave an adequate clinical description of scarlet fever and who traced the course of an epidemic. This epidemic was probably the first one of scarlet fever to occur among the English colonists of North America, over a 100 years after the first settlement of the Puritans. At the time Boston had a population of about 12,000, but the country was still sparsely settled. There was a virgin soil in which the disease ran its course uninfluenced by immunity from previous attacks. Douglass says, "This distemper did emerge May, 20 1735 in Kingston Township, 50 miles eastward from Boston; it was no foreign importation, Kingston being an inland place of no trade or considerable communication." It is to be noted, however, that scarlet fever was prevalent in Great Britain and on the continent of Europe at this time. The first case was in a child who died after three days illness. About a week later in another family about four miles distant, three children were successively seized and died also on the third day. The disease gradually spread in the township, seizing families, here and there and of the first 40 persons affected none recovered. The disease was "vulgarly called the throat illness, or a plague in the throat." Some were "called a scarlet fever." "Some died of a sudden or acute necrosis; but most by a symptomatic affection of the fauces and neck, that is by sphacelations or corrosive ulcerations in the fauces or by an infiltration and tumefaction in the chops and forepart of the neck, so turgid as to bring all upon a level between the chin and sternum, occasioning a strangulation of the patient in a very short time." As the affection spread into neighboring townships it took a milder form. It appeared in Boston about August and by the end of September had occurred in several parts of the town with no fatalities. In October, a case ended fatally, and in November it spread more widely, especially among children and several died. The epidemic reached its height in Boston the second week of March, when there were 24 burials as contrasted with nine or ten in corresponding weeks of other years. Douglass says the disease was more fatal in certain families, some burying all their children—in one case eight. At Hampton Falls 27 persons died in five families. The cases in Boston were usually milder than those in the country to the east where the epidemic began. In some country towns, of those affected one in three died and scarcely ever less than one in six. In Boston about 4000 persons had the disease i.e., about one-third of the population, of whom one in 35 died. Douglass' enumeration of the symptoms of the disease is very lucid and complete and corresponds very closely to those which have been noted by modern writers. Few of the symptoms and complications with which we are familiar failed to be noted by him. He recognized mild as well as severe cases. He says he "anatomically inspected persons who died" but gives no details of his findings. The only other attempt to study this disease post-mortem of which I have found a record up to this time was by Doringius, a friend of Sennertus.[106] During 1735 and 1736 the disease spread over New England. Fitch[33] tabulates 984 deaths from the "throat-distemper" occurring in the towns and townships of New Hampshire during 14 months of 1735–1736. Extension gradually occurred westward, and it was two years before the affection reached the Hudson River, 200 miles west of Kingston. The disease soon prevailed in all the colonies along the Atlantic coast and in the West Indies. Whether the disease extended to the southern colonies from New England or was directly imported from Europe is impossible of solution.

From this time scarlet fever was more or less prevalent in this country, and at times extensive epidemics occurred. Rush[103] describes an epidemic in Philadelphia in 1783–1784, and subsequently he speaks of outbreaks in 1784 to 1787. Webster[120] speaks of an epidemic of scarlet fever in Philadelphia in 1789–1790 which did not spread to the northern states until two years later. Between 1791 and 1793 scarlet fever spread to the settlers of Kentucky and Ohio. Drake[28] says that "in Kentucky where it was extremely fatal, it was universally called putrid sore throat." "At Marietta and Bellpre, the oldest settlements of the state of Ohio, it was most dreadfully destructive among children and young persons, attacking and destroying nearly all the former. Five or six in some cases dies out of a single family. In many instances parents lost all they had." "It is worthy of remark that at the time of this epidemic the country was an almost unbroken forest, the immigrants living in open cabins and subsisting on a simple diet."

Isolated epidemics occurred during the first quarter of the nineteenth century in Kentucky and Ohio. In the second quarter of that century Drake says "it may be regarded as one of our epidemics, having, as I suppose, at no time been absent from the valley of the Mississippi and the Lakes." He also says, "In my personal intercourse with physicians I scarcely converse with one north of the 33 degree of latitude who had not seen the disease epidemic once or several times, though many south of that parallel had never met with it." Drake describes the slow spread of the disease from one place to another, the subjects in one place usually being exhausted before it appeared in some neighboring village. The slow spread of scarlet fever noted by all these earlier writers is explained by the limited intercourse between communities because of inadequate means of travel. When the first epidemic of scarlet fever appeared in New England, the disease was prevalent in Great Britain and on the European continent. It was only when it had assumed epidemic proportions and appeared in London that it called forth any adequate description by British physicians. In 1748, John Fothergill,[34] a young London doctor, published "An Account of the Sore Throat Attended with Ulcers, etc." In a footnote he says, "In the Med. Essays, there is an extract from Dr. Douglass' description of an Epidemic Fever that raged in New

England some years ago very much resembling this disease; but that it was the same I cannot determine, having not seen the Treatise itself." Fothergill's description of the disease as observed in and near London was so excellent and attracted so much attention that the appellation "Fothergill's sore throat" was long applied to the severe forms of ulcerative angina. He laid little stress on the cutaneous eruption and failed to recognize the disease as scarlet fever. He recognized the identity of ulcerative or gangrenous sore throat observed in London as identical with the Spanish "Garrotillo" of the sixteenth and seventeenth centuries, and with the morbus strangulatorius, etc., of the Italians of the early part of the seventeenth century. Creighton[17] states that this identity had been previously recognized by Letherland whose erudition was adopted by Fothergill. Munk[83] says that "much of the valuable matter in Doctor Fothergill's account of the putrid sore throat is generally allowed to have been derived from Letherland." Fothergill in his preface says "There are several of the Faculty, who, I readily acknowledge, have it more in their power to give the public satisfaction on this subject than I have," but mentions no names. In the fifth edition of his work he acknowledged his debt to Letherland.[35]

Cotton[16] in 1748 observed "a particular kind of scarlet fever" which appears to have been the same disease described by Fothergill and others, but his observation failed to attract attention and the credit of definitely recognizing the severe and mild cases as forms of one disease has usually been given to Withering.[125]

In 1757 Huxham[53] described "the Malignant Sore Throat," and the skin eruption is included in his description of the disease. Withering,[125] in 1779 wrote "An account of the scarlet fever and sore throat, etc." He described the disease very completely and made a formal distinction between scarlatina anginosa and angina gangrenosa or ulcerated sore throat. In a new edition in 1793 he said, "From the most assiduous attention to this disease during a period of 15 years —I am now persuaded that the scarlatina anginosa and the angina gangrenosa constitute but one species of disease." While Withering was not the first to recognize the different types of scarlet fever as being but various manifesitations of one disease, still he was largely instrumental in bringing this forcibly before the profession.

After scarlet fever had been accurately described much confusion between it and diphtheria remained. The separation of the two diseases from clinical appearances was very difficult, especially since severe cases of diphtheria resembled so much the angina of some severe cases of scarlet fever. By the accurate observations of Bretonneau[10] diphtheria was sharply differentiated from the angina of scarlet fever on anatomical grounds, but it was impossible to certainly exclude the concomitant presence of the two diseases until the diphtheria bacillus had been identified and bacteriologic methods in the diagnosis of diphtheria had been introduced. During the last half of the nineteenth century epidemics of scarlet fever occurred in the cities of Europe and America, and it constantly was present in endemic form. It always appeared in mortality statistics and frequently extended from the cities to the country.

Epidemiology.—Natural immunity to scarlet fever exists in a large proportion of individuals. Under usual conditions it is difficult to determine just how prevalent is natural immunity. In modern times opportunities to observe epidemics of scarlet fever in groups of individuals of all ages who never had a previous attack have been rare. Such ideal conditions prevailed in the Farge islands when Hoff[50] made his observations in 1873 to 1875. For 57 years previous to introduction at that time, none of the inhabitants had been in contact with scarlet fever. In the chief town of the island, Thorshavn, there were 925 inhabitants, of whom 619 lived in dwellings infected with scarlet fever. Of these latter 237 or 38.3 per cent. contracted the disease. Hoff's figures are also of interest as indicating that natural immunity is little influenced by age up to 20 years. Of the persons living in infected homes, 75 per cent. of those between 15 and 20 years contracted the disease, as compared with 64 to 68 per cent. at earlier periods. Between 20 and 40 years, less than 25 per cent. of those exposed were infected, and in individuals above 40 years the instances of infection were relatively very few (Table 1). Of infants about the same proportion contracted the disease as did those of greater ages.

Table 1.—Scarlet Fever in Thorshavn
Copied from Jürgenson

Age	Total population	Living in houses with scarlet fever	Attacked by scarlet fever	Percentage of those living in infected houses who develop the disease
0 to 1 year	17	12	8	66.6
1 to 5 years	74	65	44	67.7
5 to 15 years	184	155	99	63.9
15 to 20 years	68	56	42	75.0
20 to 40 years	299	171	40	23.4
40 to 60 years	193	105	3	2.9
Over 60 years	90	55	1	1.8
Total	925	619	237	38.3

McCollom[75] says that "contrary to the generally received idea, nursing infants are particularly susceptible" and that "the only reason why more infants do not contract scarlet fever is the fact that they are not exposed to such an extent as older children." The relatively small number of cases of scarlet fever in infants among series of notified and hospital cases has often been accepted as evidence of relatively insusceptibility at that time of life. It apparently only indicates that infants are not affected with scarlet fever so frequently as older children because their opportunities for infection are necessarily more restricted. The incidence of scarlet fever at different ages is given in public health reports. These illustrate its distribution in a population among which scarlet fever is constantly present in an endemic and at irregular intervals in an epidemic form. Less frequent occurrence in the infant and in the young adult is largely due to absence of opportunity for infection in one case and to immunity from previous infections in the other.

From a statistical study Donnally[25] finds that nearly half of all cases of scarlet fever occur in children three to seven years of age, being quite evenly distributed at about 10 per cent. in each of these years. Somewhat over 1 per cent. of cases occur in children under one year of age, the incidence rapidly rising to three years, where it remains level for five years, falling by 15 years to about 1 per cent. Between three and seven years of age, about two out of three children contract scarlet fever if exposed in their homes.

Large statistics seem to indicate that more females have scarlet fever than males. That this is not due to greater susceptibility but to a larger number of females in population has been shown by Donnally who calculated the number of cases of scarlet fever per 1000 males and females in the population and found that the morbidity rates thus obtained for the two sexes are almost identical. He found that during the first four years of life boys are more susceptible to the disease, while between 5 and 15 years girls are distinctly more affected.

Morbidity.—Most of the accurate available statistics of scarlet fever throughout the world during the last half century have been assembled by Donnally. They show that in all the countries represented, from 1.8 to 4.6 cases of scarlet fever to each 1000 of population have occurred in the average year (Table 2).

TABLE 2.—MORBIDITY AND CASE FATALITY OF SCARLET FEVER IN VARIOUS COUNTRIES
Copied from Donnally

	Time	Number of years	Annual populations (aggregate)	Cases per 1000 population	Cases	Deaths	Deaths per 100 cases	Deaths per 10,000 population
Eight American cities	1873–1913	41	177,047,815	2.8	500,093	50,700	10.1	2.83
Paris	1896–1910	15	40,070,803	1.8	72,189	2,142	3.0	0.54
Nuremberg	1890–1913	22	5,650,000	3.3	18,557	1,003	5.4	1.78
Norway	1867–1910	44	....	2.5	233,587	18,566	7.9	1.98
Russian Empire	1893–1910	14	....	2.0	3,793,453	845,641	22.3	4.46
England and Wales	1892–1911	17	268,253,879	4.6	1,231,018	41,192	3.3	1.51
Prussia	1902–1912	11	....	...	787,476	59,079	7.5	
Italy	1888–1910	23	....	....	428,541	93,094	21.7	
Japan	1897–1912	16	....	....	8,882	1,452	16.3	

Figure 30 shows the annual morbidity rate for scarlet fever in old New York for 39 years. While there has been some variation in individual years, the prevalence of scarlet fever has remained quite constant throughout the period, each decade showing about the same proportion of cases. Donnally's[25] figures (Table 3) for the other large American cities correspond closely to those for New York.

TABLE 3.—MORBIDITY AND CASE FATALITY OF SCARLET FEVER IN EIGHT AMERICAN CITIES

	Time	Number of years	Annual populations (aggregate)	Cases per 1000 population	Cases	Deaths	Deaths per 100 cases	Deaths per 10,000 population
Boston...........	1877–1912	36	18,051,097	2.9	52,246	3,755	7.2	2.09
Providence........	1884–1913	30	5,105,611	3.2	16,135	1,141	7.1	2.27
New York (old)...	1874–1912	39	71,852,353	3.2	229,071	27,889	12.2	3.90
Brooklyn.........	1873–1912	40	38,294,166	3.2	122,928	13,294	11.0	3.52
St. Louis..........	1887–1911	25	14,456,089	1.9	27,213	1,625	6.0	1.14
Philadelphia......	1900–1912	13	18,862,594	1.9	35,204	1,876	5.3	1.01
Washington.......	1892–1913	22	6,505,482	1.46	9,476	238	2.5	0.38
Montreal.........	1905–1913	9	3,722,423	2.1	7,820	684	8.7	1.83

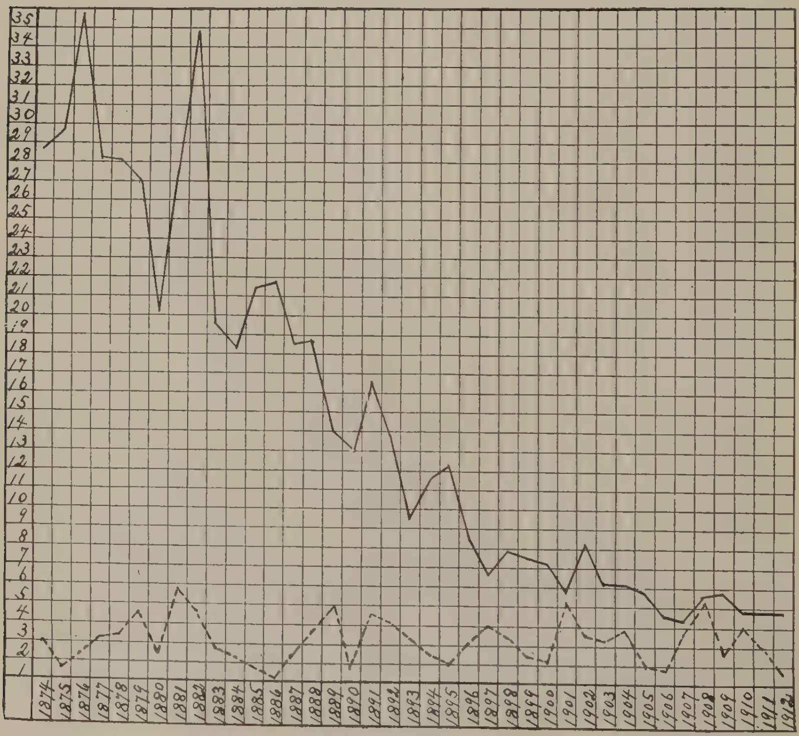

FIG. 30.—Case fatality and morbidity rates in calender years in old New York (1874–1912). Solid line—number of deaths per 100 cases of scarlet fever. Dash line—number of cases of scarlet fever per 1000 population. Figures from Donnally.)

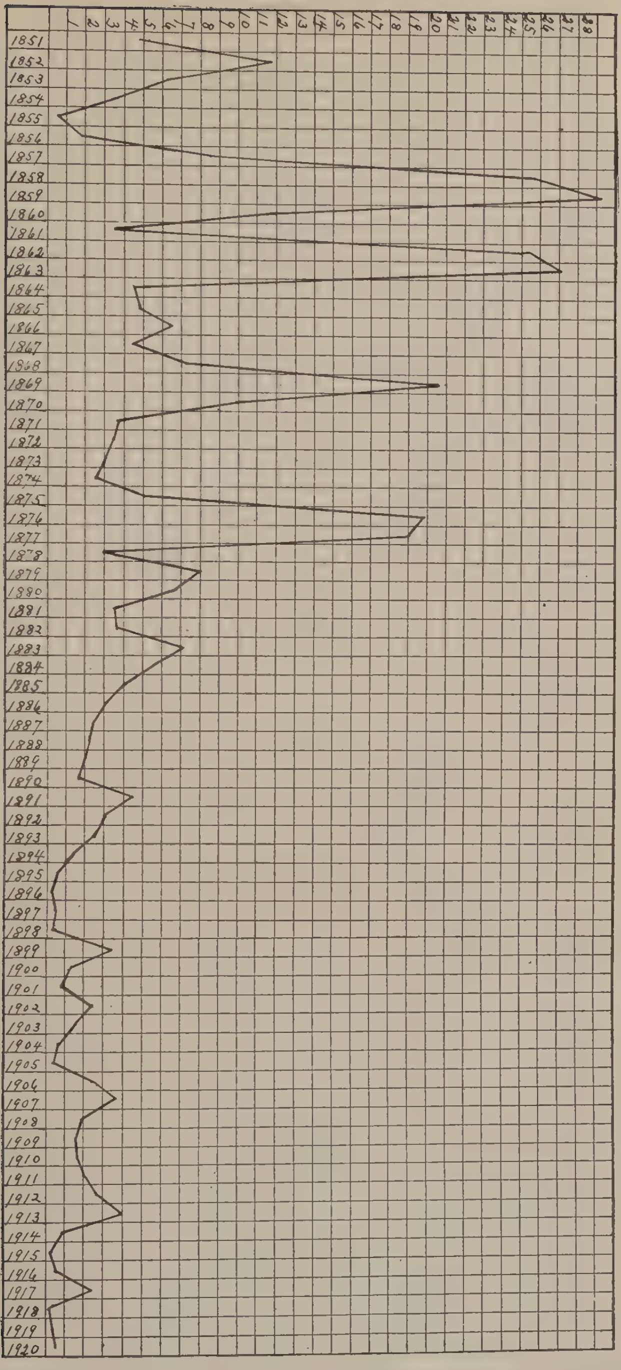

FIG. 31.—Deaths from scarlet fever in Chicago per 10,000 of population for seventy years, 1851–1920.

He thinks it probable that the more thorough notification of scarlet fever in recent years may be a factor in keeping the morbidity rate approximately level. "In Norway, where notification has been of longest duration and most thorough a reduction in the incidence of scarlet fever has been observed."

Fatality.—While there is little evidence of any considerable decrease in the prevalence of scarlet fever, the death-rate has shown a steady decline during the past 50 years. Figure 31 shows the ratio of mortality of scarlet fever per 10,000 of population in Chicago for 68 years, 1851–1918. In Fig. 30 a similar curve for old New York from 1874 to 1912 is shown. Curves of the mortality rate from scarlet fever in the various American cities would be very similar. In New York city the death-rate from scarlet fever per 10,000 of population from 1875 to 1884, was 9.15; from 1885 to 1894 4.91; from 1895 to 1905, 2.4. In Chicago the death-rate from scarlet fever per 10,000 inhabitants from 1851 to 1860 was 10.22; from 1861 to 1870, 11.28; from 1871 to 1880, 7.47; from 1881 to 1890, 3.53; from 1891 to 1900, 1.81; from 1901 to 1910, 1.77; and from 1911 to 1918, 1.65. The mortality statistics of the census bureau give the death-rate from scarlet fever per 100,000 of population in the United States as 11.0 in 1901–1905, 10.6 in 1906–1910 and 6.9 in 1911–1915. In the rural portion of the registration states the death-rate is from 30 to 75 per cent. of that in the cities of the same states.

Among the chief causes of death in Chicago from 1857 to 1866, scarlet fever occupies the fifth place. The following two decades it fell to seventh and then to ninth place, and in the two decades from 1887 to 1905 it occupied the twelfth place.[14] In hospitals the case fatality varies much in different years and epidemics. As shown in Table 4 the deaths per 100 cases in Durand Hospital* varied from 1.27 to 8.76 over a period of 10 years. The average death-rate per 100 cases in Durand Hospital for 10 years (1913–1922) was 3.62; in Providence City Hospital[95] for six years (1910–1915), 4.9; in Alexandra Hospital,[78] Montreal for four years (1906–1909), 8; in the Children's Clinic of Strassburg University[64] for 29 years (1874–1902), 12.1. The figures correspond closely with the case fatality rates in public health reports in recent years which fluctuate from about 1.5 to 10 per cent.

Donnally[25] says that "the most striking fact about the case fatality of scarlet fever in the past half-century has been its consistent general and marked reduction." The case fatality in American cities, which ran from 15 to 37 per cent. in the seventies of the nineteenth century, has usually varied from 1.5 to 10 per cent. in the first decade of the twentieth century. There seem to be several factors entering into the determination of the lessened case mortality of scarlet fever. It is generally conceded that the virulence of scarlet fever has grown less, and

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* Because of my familiarity with cases treated in Durand Hospital of the John McCormick Institute for Infectious Diseases since its establishment I have made very free use of this material to illustrate the present article.

TABLE 4.—SCARLET FEVER IN DURAND HOSPITAL 1913–1922

Years	Cases	Deaths	Deaths per 100 cases
1913	217	19	8.76
1914	193	14	7.25
1915	245	7	2.86
1916	316	4	1.27
1917	284	12	4.23
1918	211	4	1.90
1919	275	8	2.91
1920	340	6	1.76
1921	241	11	4.56
1922	273	9	3.30
Total................	2595	94	3.62

TABLE 5.—COMBINED SCARLET FEVER STATISTICS FOR SIX YEARS IN PROVIDENCE CITY HOSPITAL (1910–1915) AND DURAND HOSPITAL (1913–1918)

Age	Cases	Deaths	Deaths per 100 cases
Under 1 year....................	13	4	30.8
1 to 2 years....................	52	7	13.5
2 to 3 years....................	147	21	14.3
3 to 4 years....................	179	9	5.0
4 to 5 years....................	241	17	7.1
Under 5 years..................	632	58	9.2
5 to 6 years....................	254	21	8.3
6 to 7 years....................	283	4	1.4
7 to 8 years....................	266	4	1.5
8 to 9 years....................	222	4	1.8
9 to 10 years..................	165	5	3.0
5 to 10 years..................	1190	38	3.2
10 to 15 years................	488	10	2.0
15 to 20 years................	186	7	3.8
20 to 30 years................	309	11	3.6
30 to 40 years................	70	5	7.1
40 to 50 years................	21	0	0.0
50 to 60 years................	6	1	16.7
Total..........................	2902	130	4.5

to this factor the lessened death-rate is probably most largely due. Other factors which undoubtedly exert an influence are the more general hospitalization of cases and the use of diphtheria antitoxin in cases complicated by diphtheria. However the greatest decline had occurred before diphtheria antitoxin was introduced.

Influence of Age upon Fatality.—All hospital statistics show a high death-rate in infants with a rapid fall during the first five years of life, then a nearly even rate for three or four years followed by a slight rise up to about 40 years. This is illustrated by Table 5 and Fig. 32 which comprise an equal number of cases from each of two hospitals in entirely different parts of the country. The fatality in those over 50 years of age again approaches that in the second and third year. Donnally's[25] studies lead him to conclude that the death-rate is from 12 to 20 per cent. during infancy and that it rapidly diminishes with each succeeding year of life until between 10 and 14 years when it is lowest, being in the neighborhood of 1 per cent. From this age on there is a slowly rising death-rate. About 90 per cent. of deaths occur in children under 10 years. In Murchison's[84] series nearly 7 per cent. occurred in infants under one year. About 64 per cent. of the deaths occurred in children under five years, and about 90 per cent. occurred during the first 10 years of life. In Chicago from 1904 to 1907, of the total deaths from scarlet fever, 5 per cent. occurred in children under one year, 58 per cent. in those under five years, and 86 per cent. in those under 10 years.

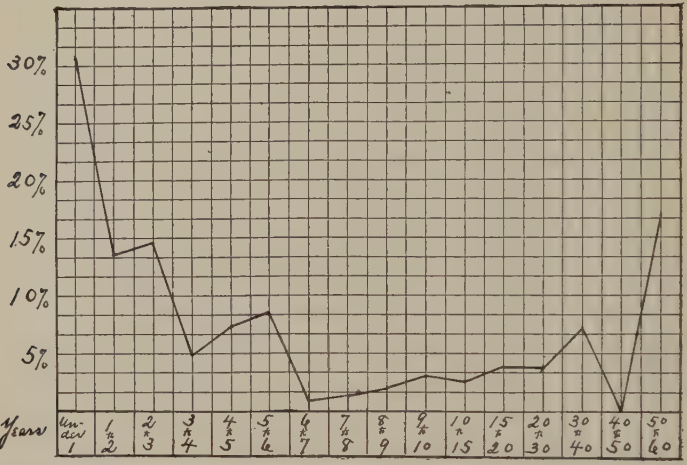

Fig. 32.—Combined scarlet fever statistics for six years in Providence City Hospital (1910–1915) and Durand Hospital (1913–1918). Solid line—fatality rate at various ages.

Sex as Influencing Fatality.—Donnally[25] studied the combined figures from Nuremburg (1890–1912), London (1894–1912) and Norway (1880–1910) as regards the influence of sex upon mortality in scarlet fever. Among 513,713 cases there occurred 20,889 deaths, of which 53 per cent. were among boys and 47 per cent. among girls. The case fatality among boys was 4.5 per cent. as against 3.67 per cent. among girls. Murchison's figures[84] for England, Wales and London from 1845 to 1861, give 75,373 deaths among males as against 73,456 among females. The excess of males concerns principally the first five years of life. Later the proportion of deaths among females becomes larger, especially when maturity has been reached. In old New York City from 1866 to 1906 the deaths from scarlet fever in the two sexes were almost equal. A preponderance of about 4.5 per hundred among males in the first five years of life was about balanced by a slight excess of females from 5 to 15 years and by an excess of about 25 per hundred among females above 15 years of age. This last fact is explained by the greater exposure to infection among women while caring for children sick with the disease.

Influence of Race.—There is a general impression that there is less susceptibility to scarlet fever among negroes and Asiatic people than among the white races. Minor[80] concluded from a statistical study that "there is a certain immunity from epidemic scarlatina existing among the negroes of the South." From a study of the statistics of the Metropolitan Life Insurance Company, Dublin[29] finds that the death-rate for colored children is about one-fourth that of the whites. According to the mortality statistics of the U. S. Census Bureau, the death-rate of scarlet fever from 1911 to 1916 in the registration cities and states of the South where there is a large colored population, was from two to five times as great as among the whites as among the colored.

Influence of Season upon the Occurrence of Scarlet Fever.—A general impression exists that the seasons of the year exert a distinct influence upon the occurrence of scarlet fever. When studied as to the time of their beginning, Hirsch[49] found that out of 289 epidemics, 73 began in winter (December to February), 61 in spring (March to May), 69 in summer (June to August), and 86 in autumn (September to November). He also found that mild and severe epidemics were about evenly distributed through the year. From his recent statistical study Donnally[25] also concludes that season itself does not influence the morbidity from scarlet fever.

When a study is made of the figures showing the morbidity and mortality from scarlet fever in cities over a number of years, the relatively large number of cases in autumn and winter contrasts strongly with the smaller number in the other half of the year. Figure 33 shows the proportion of cases and of deaths from scarlet fever falling in the various months of the year over a period of seven years (1912–1918) in Chicago. Figure 34 shows the mortality curve for scarlet fever in Chicago as distributed through the months during a period of 40 years (1878-1918). The statistics of other cities would furnish data for the construction of similar curves. We must, therefore, conclude that it is usual for the greatest proportion of deaths to occur during the autumn and winter.

Because the season of lowest incidence of scarlet fever corresponds more or less closely with the usual vacation period in schools it was not unnatural to conclude that the former was dependent upon the

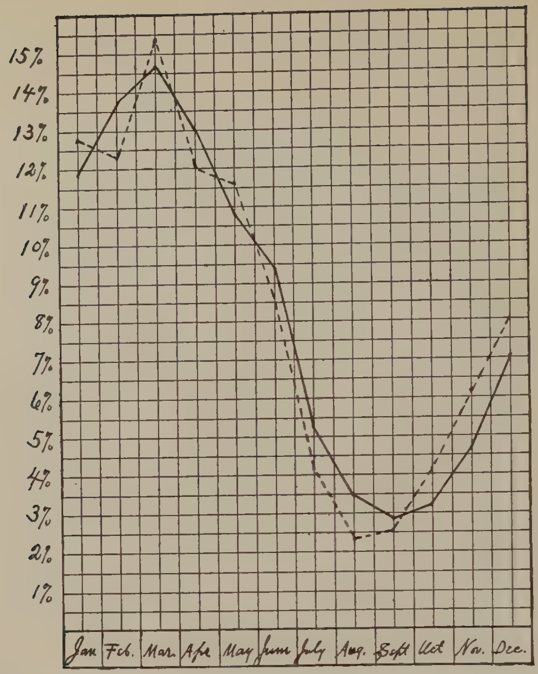

FIG. 33.—Percentage of mortality from, and of reported cases of scarlet fever in Chicago for seven years (1912–1918) falling in various months. Solid line—mortality. Dash line—reported cases.

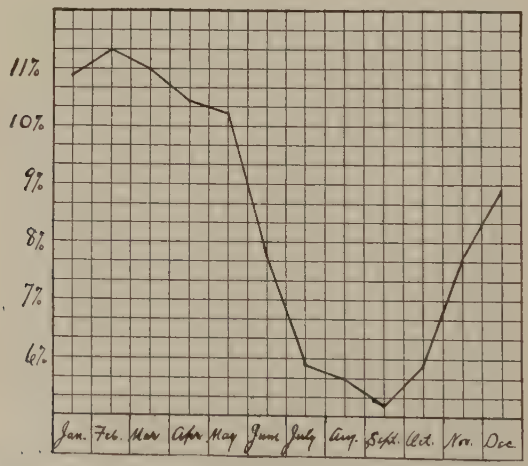

FIG. 34.—Percentage of deaths from scarlet fever in Chicago for 40 years (1878 to 1918) falling in various months.

latter. Kerr[59] and Chapin[13] from statistical studies conclude that scarlet fever is rarely spread in schools and that the great mass of cases originate independently of school conditions. Jordan[57] after a careful examination of the weekly number of reported cases of scarlet fever in Chicago from 1908 to 1912 was unable to detect any well-marked variation in the number of cases at the dates of the opening and closing of schools in September and June or at the time of the Christmas and spring holidays. Bernhard[5] studied the fatality statistics of Berlin and of six principal Rhenish cities for a period of 10 years (1901–1910) as regards the influence of vacations on diphtheria and scarlet fever. He concludes that while schools may be a factor in the spread of scarlet fever, it is not the most important factor and that living conditions in winter favor the spread of contagion. The decline in scarlet fever begins before the end of the school year, and the rise may begin toward the end of vacation.

While the association of children in school doubtless contributes to the spread of scarlet fever, the seasonal prevalence in winter is more readily explained by other factors. Among these are the lack of ventilation, crowding and other unhygienic conditions in the home, public vehicles and places of congregation. Also, general catarrhal conditions of the upper respiratory mucous membranes probably increases susceptibility to infection.

The effect upon the mortality from scarlet fever when it is immediately preceded by another infection is sometimes very marked. This is shown very emphatically by the study of Wilson[124] of infectious diseases in children among immigrants with special reference to cross infection. Cases in which scarlet fever followed measles showed a case fatality of 34 per cent. and those in which scarlet fever followed diphtheria a case fatality of 80 per cent. as compared with a fatality rate of 16.6 in all cases of scarlet fever. The same study also shows how scarlet fever acts to increase the fatality of other diseases which follow it. Cases in which measles followed scarlet fever had a fatality rate of 26 per cent., and those in which diphtheria followed scarlet fever had a fatality rate of 38 per cent as compared with rates of 8.7 for measles and 25 per cent. for diphtheria when not preceded by scarlet fever. Cosgrave after a study of the recorded cases of combined typhoid fever and scarlet fever infection concludes that the coexistence of the two diseases does not seem to add to the danger of either.

Modes of Spread.—Since we are unacquainted with the cause of scarlet fever and are unable to determine its presence in secretions and excretions, our ideas as to the manner of spread of the disease must be founded upon clinical experiences and upon what we know of the spread of other diseases with known etiology. In any case our theories are not final and must be adjusted to correspond to added information. It is generally believed that the virus of scarlet fever is present in the secretions from the involved mucous membranes of the nose, throat, accessory nasal sinuses and middle ear, and in discharges from suppurating glands. The idea, formerly generally held, that the cause of the disease was in the scales from the skin has now been largely discarded. Experience, especially of English isolation hospitals, seems to indicate that the scales are not to be feared as disseminators of the disease. The release from quarantine of desquamating patients who are free of discharges from the nose, ears, etc., does not appear to be followed by new infections.

If these conceptions of the location of the virus of the disease are correct, we must look upon the transmission of infected secretions as the important factor in spreading the disease. The transfer of infection may be through direct contact between the sick and others or through the agency of a great number of intermediary carriers. Among the latter may be enumerated foods and drinks; hands, hair and clothing of attendants and others, eating utensils, soiled dressings, bedding, clothing, handkerchiefs, towels, toys, books, pencils, and pet animals. While animals are not known to suffer from scarlet fever, it is readily conceivable that domestic animals, especially pets, may be carriers of infectious matter. The seasonal distribution of the disease excludes such insects as mosquitoes as the transmitters of the infection. Biting insects which are present throughout the year such as flees are probably excluded since their distribution is not such as to explain the spread of the disease. The widely distributed domestic bed bug cannot be entirely freed from suspicion. The domestic fly would apparently be able to distribute the infectious materials, and, as in typhoid fever, when contaminated by infected secretions could easily introduce the same into foods of various sorts.

Aerial transfer of infection probably does not play a large part. There is no evidence to show that those living near hospitals which care for patients with scarlet fever are more frequently attacked. The buildings of the old City Hospital in Edinburgh are surrounded by lofty tenements, literally packed with children, Ker[60] reported that scarlet fever was no more common in this population, living so close to scarlet fever wards which often contained over 300 patients, than in other districts of the same class in the city. McCollom[76] has given the number of cases of scarlet fever which occurred in 1896 within various distances from the South Department of the Boston City Hospital. No cases were within one-eighth of a mile, and at various fractions of a mile the numbers were about equally distributed. Similar experiences have been general. Aerial transfer at short distances may occur but is probably infrequent. In forced expiratory efforts particles of infected saliva are thrown from the mouth, and if they lodge in the throat or nose of a susceptible person may cause infection. This form of infection demands that the infected individual be brought in close proximity with others, as occurs when an attendant cares for the patient or when persons are crowded in small rooms or in public conveyances.

Milk is the only food which conveys scarlet fever with any frequency.

Milk-borne Scarlet Fever.—So many outbreaks of scarlet fever have been accurately traced to infected milk that there is no doubt of the connection in many instances. While the relative proportion of cases due to infection through milk is not great, the aggregate of such cases is not inconsiderable. Busey and Kober[11] in 1895 made a compilation of 59 epidemics of scarlet fever spread by milk. Trask[117] in 1908 tabulated 51 additional epidemics, 25 occurring in the United States and 26 in Great Britain. Power and Klein[62] attempted to connect outbreaks of scarlet fever with diseased conditions of cows' udders, but subsequent observers have not been able to substantiate their findings. It is probable that the milk contamination is always due to a human factor, the virus of the disease being introduced into the milk by a person who is suffering from scarlet fever or carries the infectious material from a human case. In Trask's series "All cases enumerated in the outbreak were reported as living in houses supplied with the suspected milk in 27 of the epidemics; a case suffering from the disease at such a time as to have been the possible source of infection was found at the producing farm, the distributing dairy, or milk shop in 35 cases, the outbreak was supposed to have been due to bottles returned from infected households and refilled without previous sterilization in three cases; the diseased person or persons were mentioned in handling the milk or milk utensils in three; the sick milked the cows in 12; the same

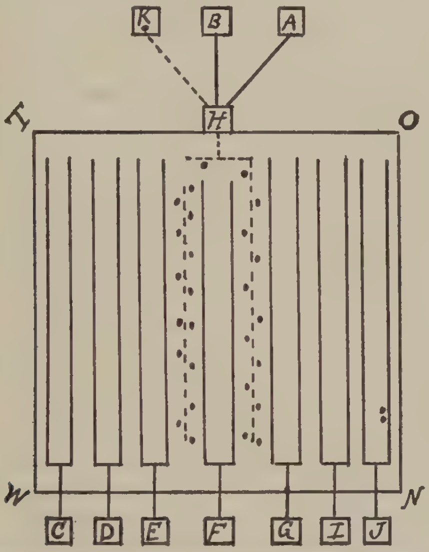

FIG. 35.—Diagram showing relation of milk routes to scarlet fever cases during outbreak at Norwalk, Conn., 1897. A, B, and K, are dairy farms selling their product to retail milk dealer H. K is the farm on which a case of scarlet fever occurred antedating the outbreak in Norwalk. The large square T, O, W, N, represents the city of Norwalk. H is the retail milk dealer among whose customers all cases but two occurred. The dash lines represent H's milk route, and each dot is a case of scarlet fever. C, D, E, F, G, H, I, and J are other dairymen having routes in Norwalk. The lines extending from them into the city represent their milk routes and are introduced to show their freedom from the disease. (Copied from Trask.)

person nursed the sick and milked cows in one; the outbreak was supposed to be due to disease of the cow in two; it was reported that measures taken upon the presumption that milk was the cause of the epidemic were followed by abatement of the outbreak in 22 cases."

An interesting illustrative case is cited by Trask[117] (Fig. 35). In November, 1897 an unusual number of cases of scarlet fever occurred in Norwalk, Conn.[109] Between October 25 and November 9, 29 cases developed. The 29 cases were distributed in 25 families and 24 homes. School infection was eliminated. Many did not attend school, and some were in families without school children. The cases were widely separated. The families were of different social positions, and contact infection seemed improbable. The only factor in common to practically all the cases was the milk supply. Twenty-seven out of 29 obtained milk from one dealer. Dealer H furnished one-eighth of the milk to the city, and 27 of the 29 cases of scarlet fever were on his route. H bought the milk from three producers. There were no cases of disease in the family of the milk dealer nor in those of two of the producers, A and B, but on the third producing farm, K, a case of scarlet fever was found. This case was a boy who developed scarlet fever on October 24. Milk from the farm was delivered by dealer H, to 300 families, of which 24 were invaded. The sale of this milk was stopped on November 7, and after November 9 the cases ceased to appear.

An extensive epidemic of scarlet fever traced to contaminated milk may also be used as illustrating the usual course followed by such outbreaks. For six weeks preceding Jan. 12, 1907 the reported cases of scarlet fever in Chicago[15] averaged 135 weekly, and the cases were quite evenly distributed throughout the city. During the week ending January 19 the reported cases jumped to 348, and reports from the suburbs to the north and west which received their milk from the same source as did the infected district in Chicago reported epidemic prevalence of the disease. Investigation in the suspected dairy district revealed a considerable number of cases of scarlet fever, five to six being in the family of a dairyman who shipped milk to a large distributing company. On January 25 all milk from the infected dairy was excluded from the market. Allowing for period of incubation, we should expect the height of the epidemic after exclusion to fall in the week ending February 2. This was the case, and, thereafter, the epidemic rapidly subsided. The cases reported January 19 were 348; January 26, 1006; February 2, 1689; February 9, 620; February 16, 380; February 23, 277. This epidemic, like most milk-borne epidemics, had an explosive onset, rose rapidly to its height and declined quite rapidly after the source of infection was removed. In epidemics spread by milk, users of milk are picked out; the well-to-do, who use milk more freely than the poor, are often specially attacked. Simultaneous cases in families are apt to occur.

It is likely that mild and unrecognized cases of scarlet fever play no inconsiderable part in the spread of the disease. Such cases have often been the source of milk contaminations. We have no means of determining whether a true carrier of scarlet fever exists. By a true carrier is meant one who harbors the virus of the disease in the throat where it continues to multiply without causing any symptoms. If such do exist they would be potential spreaders of infection.

Fomities may be carriers of infection. Contaminated clothing, bedding, letters, books, toys, etc., have been said to produce infection after months and sometimes several years. Certain houses have also acquired a reputation for harboring the virus of scarlet fever for long periods. There is reason for believing that the virus of scarlet fever retains its virulence in dried secretions, a very long time when protected from light. In a Chicago hospital a ward used for several years for scarlet fever cases had a tile floor in which many tiles were loose. Subsequently this ward was used for general medical cases, and on several occasions when parts of the floor were torn up to repair plumbing, cases of scarlet fever developed among the patients in the ward as well as in a nurse and an orderly.

Incubation Period.—Instances of scarlet fever developing after a single exposure in which an earlier or later exposure can be certainly excluded are uncommon. On this account it has been difficult to arrive at definite conclusions as to the length of the period of incubation. Good observers have recorded the time at less than 24 hours and as late as 21 or even 28 days. Holt,[51] in 1896, collected 113 cases from the medical literature and from personal observations in which circumstances were such as to make it possible to determine the exact length of incubation. His figures are as follows:

24 hours or less	6
2 days	15
3 days	28
4 days	25
5 days	6
6 days	15
7 days	8
8 days	2
9 days	5
11 days	1
14 days	1
21 days	1

Of these 113 cases, 87 per cent. occurred after two to six days incubation, and very few after a week. He believed that a short incubation is more frequently seen in severe than in mild cases. Klose[64] observed four cases in which he was able to make observations upon this point. The incubation periods were three, four, six, and seven days. Jochmann[55] says that the incubation is very variable, as a rule four to seven days, but in single cases less than 24 hours. Thomas[113] makes practically the same statement. Ker[60] says: "It may be asserted with some confidence that the latent stage of scarlatina is invariably a short one. We may take it that the incubation period never exceeds seven days and that it is very seldom longer than four. The vast majority of patients take from two to three days to develop their first symptoms. In some cases I believe that the stage is certainly less than 48 hours, but anything under 24 must be extremely rare." It would not be profitable to quote similar statements from other sources. There is a general agreement that the period of incubation is quite variable but that in most cases it is less than a week and often two to four days. In a few instances we have observed the development of scarlet fever in pupil nurses within 24 hours after they entered the contagious disease hospital, and when there had been no known previous exposure.

Etiology.—That scarlet fever is caused by a living agent or virus which passes from one individual to others seems evident, but no convincing demonstration of this virus has been made. The insusceptibility to scarlet fever of experimental animals deprives the investigator of one of the principal aids in his study. Experimental inoculation of scarlet fever in man is also attended with great difficulty. This is emphasized by the failure of Dick and Dick[21a] to produce a single typical case of scarlet fever although all sorts of materials from persons sick with the disease were inoculated into young persons who gave no history of previous attacks. After a critical study of the reports of all such efforts, Hektoen[47a] concludes that "it is exceedingly doubtful whether a simple positive result had been obtained."

Those who have studied the disease bacteriologically have always been impressed by the prominence of streptococci, which are present not only in the inflamed throat but also in association with most of the complicating inflammatory processes and often in the blood during life.

Crooke[18] in 1885 reported finding streptococci in the tissues of the neck and in the organs of persons who had died from scarlet fever. In 1887 Klein[61] undertook to show that cocci cultivated from certain lesions of the cow's udder were identical with those which he cultivated from the blood of cases of scarlet fever. His conclusions were attacked by other English and German investigators and were not generally accepted.

Raskin[96] reported the bacteriologic study of 92 cases and concluded that streptococci caused most complications but that they had no causal relation to the primary disease.

Baginsky and Sommerfeld[2] reported bacteriologic examinations of 363 cases. They concluded that in all cases of scarlet fever streptococci are present, sometimes in pure culture, and always in preponderance. They considered their constant presence significant but did not decide that they had specific characters.

Jochmann[54] cultivated streptococci from the blood during life from 25 out of 161 cases. All the patients yielding positive cultures died.

Hektoen[47] made cultures from the blood during life from 100 cases of scarlet fever and in 12 secured growths of streptococci. Nearly half the cases were mild, and positive cultures were secured from four of them, but severe cases yielded a higher proportion of growths.

The works of the investigators who have been mentioned stand as milestones along the road which has been traveled by a large number of workers who also have left more or less valuable contributions all along the way. The relationship born by the streptococci, which are almost always if not always present in scarlet fever, has been a matter of much dispute, an effort to throw light upon this has been made by searching for specific anti-streptococcus bodies in the blood in scarlet fever. Koessler and Koessler[66] brought together the evidence upon this point and concluded that it is clear that the serum of scarlet fever patients contain antibodies for streptococci but that this does not solve the problem whether the streptococcus is the primary agent of the disease or a secondary invader.

Jochmann[54] after a review of all the evidence regarding the relationship of streptococci to scarlet fever reached the conclusion that streptococci are the most common and dangerous cause of the secondary infections of scarlet fever but are not the cause of the disease itself.

Hektoen[46] after a careful discussion as to whether scarlet fever is a streptococcus disease concluded; "Thus it becomes evident that there are rather definite obstacles to the unreserved acceptance of the streptococcus theory of scarlet fever. The view that the specific cause of scarlet fever is not known and that the streptococcus is a concomitant or secondary invader, for the growth and activity of which the conditions in this disease are peculiarly favorable, seems to me to harmonize better with the facts now at hand." Some more recent studies have served to again arouse interest in the relationship of streptococci to scarlet fever. Hemolytic streptococci from acute cases of scarlet fever were injected into animals and the serums of these animals were subsequently tested for anti-streptococcus bodies. Tunnicliff[117b] found that the serum from such immunized animals contained opsonins and agglutinins for the hemolytic streptococci that prevail in the throat and complicating lesions in scarlet fever, but not for hemolytic streptococci from other sources. These observations were confirmed by Bliss[7a] who found that the hemolytic streptococci from the throats of patients with scarlet fever were usually agglutinated by anti-streptococcic sera made with streptococci isolated from scarlet fever, but not by sera made with streptococci from other sources. The scarlatinal strepococci were usually not agglutinated by anti-streptococcus sera made with streptococci from non-scarlatinal origin. Bliss later demonstrated streptococci, which were agglutinated by the scarlatinal anti-streptococcus serum, in the throat of carriers of scarlet fever. Similar results were also reported by Gordon.[40a]

These observations suggest the association with scarlet fever of a distinct biologic group of streptococci. They do not however establish an etiologic relationship between them and the disease. If anyone considers the abundant opportunities in the throat in scarlet fever for the entrance into the lymph stream and so into the blood of bacteria which enter the throat from various sources, one should not be surprised that a variety of bacteria may be cultivated from blood on many occasions. Dick and Henry[22] made anaërobic cultures from the blood in 24 cases of scarlet fever and obtained growths in 20. Nine varieties of organism were grown. They conclude that during the acute stage of scarlatinal angina, organisms enter the blood stream in considerable number and are excreted in part at least in a viable condition through the kidneys. In view of these findings one can attach but little significance to occassional reports of the finding of bacilli in the blood of a few cases. Mallory[74] found in the skin of four cases of scarlet fever what he believed to be protozoa having an etiological relation to the disease. The next year Field[32] described the same appearances in the skin of measles, also, and explained them as part of the protoplasm of the epithelial cells so changed in chemical nature that it took on unusual staining properties. Other microscopic appearances in the tissues of persons who have died of scarlet fever have been described by Gamaleia[39] and others, but their significance is a matter of much uncertainty.

Pathological Anatomy.—The gross lesions of scarlet fever are slight, and little is found in the dead body which is characteristic of the disease. Most abnormal conditions observed are secondary and do not differ materially from similar ones which occur during the course of other infectious diseases. Pearce[91] as the result of careful post-mortem study of 23 cases of scarlet fever, more than half of which died on the second and third day, states that the only gross lesions characteristic of scarlet fever are hyperplasia of the lymphatic apparatus, not only of the large lymph-nodes found in the subcutaneous tissues but also the lymph nodules of the alimentary canal and respiratory passages, cloudy swelling or fatty degeneration of the liver and kidney, and occasional enlargement of the spleen. All other lesions he considers as sequelæ or the result of local or general infection. The most important inflammatory conditions which he found in the order or their frequency were acute bronchopneumonia, acute inflammation of the middle ear with or without extension to the mastoid cells, suppuration of the cervical lymph-nodes, acute pleuritis and inflammation of the antrum of Highmore. The less frequent complications were abscess of the lung, ulceration and abscess formation in the upper respiratory tract, acute endocarditis, inflammation of the sphenoidal sinus and metastatic abscesses of the kidneys. The histological alterations as disclosed by Pearce's study were quite characteristic. In the skin, tongue and mucous membrane of the mouth and pharynx the vessels are congested, the lymphatics dilated, and the epithelial and subepithelial tissues, particularly the former, infiltrated with polymorphonuclear leukocytes. The changes are most marked in the tongue. The most marked cell change is the production of plasma cells in the spleen, lymph-nodes and lymphoid tissue throughout the body.

Symptoms.—Onset.—The onset of scarlet fever is usually very abrupt. Sometimes there is a brief period of indisposition preceding the acute symptoms. The child may go to school in usual health and be taken with acute symptoms while at his tasks, or he retires at night in apparent health to be awakened by acute illness. In a large number of cases nausea and vomiting are initial symptoms. Rush[103] said that this was so invariably present that he considered it a pathognomonic sign of the disease. The frequency of this symptom was noted by others of the earlier authors. McCrae[78] observed vomiting at the onset in 61 per cent. of his 850 cases. Bell[4], and Welch and Schamberg[123] noted it in about 50 per cent. of their cases. McCollom[75] says that of 5000 cases observed in the South Department of Boston City Hospital nausea and vomiting as an initial symptom occurred in about 80 per cent. Since initial nausea and vomiting occur in about three-fourths of the cases it becomes a very important diagnostic sign. The vomiting may be associated with diarrhea. This was noted by McCrae[78] in 6 per cent. of his cases. Usually there is constipation.

Sore throat is one of the most constant of the early symptoms. In McCrae's series it was present in 77 per cent. The patients complain especially of pain upon swallowing.

Fever appears early, and with it there is often headache and pain in the limbs and back. In young children the sickness may be ushered in with convulsions. In older children chilliness is frequent, and adults, especially, may have distinct chills.

Cutaneous Phenomena.—After the initial symptoms enumerated have appeared in various degrees of severity and combinations, the specific signs of the disease rapidly develop. The most characteristic and constant of these is the eruption. The exact time after the onset when it is seen varies somewhat. In 685 of McCrae's[78] cases, in which exact notes of the onset of the rash were made, it was as follows:

First day	26.7 per cent.
Second day	43.2 per cent.
Third day	20.8 per cent.
Fourth day	6.0 per cent.
Fifth day	2.0 per cent.
Sixth day	less than 1 per cent.

Klose[64] gives the length of the prodromal period for 192 cases in which it could be learned with accuracy as follows:

Less than 24 hours (2 to 24)	77 (40.1 per cent.)
1 day	72 (37.5 per cent.)
2 days	27 (14.1 per cent.)
3 days	10 (5.2 per cent.)
4 days	1 (0.5 per cent.)
5 days	4 (2.1 per cent.)
6 days	1 (0.5 per cent.)

McCollom[75] says that the characteristic eruption may appear two or three hours after the vomiting or may be deferred for 12 to 14 hours, and in rare instances does not appear for 24 hours. While the eruption usually develops early there are undoubtedly cases in which it fails to appear until as long an interval as three to five days have passed.

The eruption usually first appears upon the chest and neck and rapidly extends over the entire surface of the body in most cases. It reaches its height in 24 to 36 hours. The distribution is variable. In cases in which the rash is marked it is universal. The face is often spared or but little affected. It is not uncommon for the eruption to be evident over the lower part of the cheeks, and it may appear upon the forehead. The region about the mouth is spared giving rise to "circumoral pallor." This sign is accentuated by the frequent marked flushing of the cheeks and temples. In milder cases the limbs may escape. McCollom[75] describes the rash as a "punctate erythema." There is a diffuse erythema of a bright scarlet color stippled with fine points of deeper red. The papillæ of the skin are enlarged in cases with well developed eruptions. The degree of erythema varies greatly usually being in proportion to the severity of the case. When very intense it obscures the punctate character of the rash. The palms of the hand and soles of the feet participate in the erythema when it is pronounced but do not show the punctate characteristic. In the axillary regions and the groins the most perfectly developed and typical eruption is apt to be seen in milder cases. Pressure with the finger tip causes a blanching of the skin, but when it is removed the color immediately returns. When the hyperaemia is marked the skin has a feeling of tumefaction and tenseness which has been compared to that in erysipelas and which Withering[125] described as resembling a boiled lobster. Huxham[53] spoke of the color as a "crimson hue, as if the skin has been smeared with juice of raspberries." The color of the scarlet fever skin varies much with the amount of pigment normally present. In individuals with fair skins it is brighter while in those with darker skins it is deeper red, almost mahogany. In Africans the skin has more of a bluish tint, and the enlarged papillæ may be prominent. In many individuals the eruption on the extremities is distinctly blotchy with portions of normal colored skin so that when seen alone it is strikingly suggestive of measles. Some cases of a considerable degree of severity do not show a general eruption, but only an atypical, largely confluent, blotchy appearance which appears especially about the knees and elbows, over the outer aspect of the thigh and in the axillary region. Graves[41] described cases with a diffuse redness about the knees and elbows although an eruption did not appear on any other part of the body.

In older writings upon scarlet fever cases are spoken of as *scarlatina miliaris* and *scarlatina vesicularis.* It is not uncommon to observe minute vesicles in the scarlet fever eruption. They vary considerably in size from those barely visible to others ⅛ in. or more in diameter. They may be very numerous and occur especially upon the chest and abdomen. We have noted the larger sizes upon the arms, hands and legs. Welch and Schamberg[123] direct attention to the mons veneris as the site of especially large vesicles of this sort apparently due to intense hyperaemia. In this region they may develop into well-marked, yellowish pustules. As these lesions are more abundant when the eruption is intense, excessive inflammatory action of the skin has been advanced to explain their occurrence.

We have noticed that marked instances of sudamina in scarlet fever occur during the summer and that such cases are more frequent in warm weather. It is likely that they are due to obstruction to the orifices of the sweat glands brought about by changes in the epidermis during the scarlet fever eruption and that they develop more often when the sweat glands are functionally active. Their distribution corresponds to sudamina unassociated with scarlet fever. It is unusual for patients to complain much of itching, but they more often speak of the skin, especially of the hands, as feeling tense and thick. The skin feels hot to the touch during the acute stage of the disease and remains dry with little tendency to sweat throughout.

It is not uncommon when the cutaneous congestion is intense to find minute petechiæ scattered throughout the eruption. This is especially apt to occur if mild injury has been done to the cutaneous vessels. If an elastic band is placed about the arm for 10 to 15 minutes being sufficiently tight to cause a blueness of the hand but not so tight as to prevent the pulse at the wrist being readily felt, there appear in the delicate skin at the bend of the elbow petechiæ of a dark color. The occurrence of this phenomenon in scarlet fever was described by Leede,[71] and it is spoken of as the Leede-Rumpel Sign. He obtained it very constantly in scarlet fever but also in other conditions. Strauch[110] found that similar hemorrhages occurred in 45 per cent. of healthy children as well as in numerous diseases. Michael[79] also studied 100 normal children and found that with Leed's technique hemorrhages were produced in 60 per cent. of normal children. These findings bear out Leede's conclusion that the occurrence of hemorrhages are only presumptive evidence in favor of scarlet, but that their absence speaks against it.

Another cutaneous sign of scarlet fever has been described by Pastia.[90] It consists of an intense continuous, linear pigmentation of the skin folds across the anterior surface of the elbow, varying in color from rose to dregs of wine and even appearing ecchymotic. It is usually single, but there may be several lines. Taubles[112] found this sign in every one of 73 cases of scarlet fever. It appeared simultaneously with the rash and lasted some days after the rash had disappeared. He also observed it in three cases of measles, one of angio-neurotic edema and one of dermatitis venenata. He failed to detect it in drug eruptives or in erysipelas. This sign would appear to be of some value in doubtful cases.

The duration of the eruption is most variable. In mild cases it is so transient at times that the diagnosis must be made upon other signs of the disease. It usually begins to fade after two or three days and has usually entirely disappeared in from 7 to 14 days. Often a diffuse yellowish tint is present in the skin after the eruption has faded.

The degree and duration of desquamation varies much in different cases. The extent of the general desquamation is in general in proportion to the severity of the eruption, being very profuse in cases with intense eruptions and very slight or absent in mild ones. In cases of moderate severity scaling begins upon the face as the eruption fades. Upon the cheeks and forehead it appears in the form of fine powdery scales, and about the same time is noticed on the ears and sides of the neck. It rapidly follows upon the chest and abdomen about the sixth day and to a less extent upon the extremities. In cases with intense eruptions the scaling may be very profuse and the scales larger, giving the surface a rough, ragged appearance. Where sudamina have been present the scales have a cup shape, leaving little depressions after they are detached. Occasionally a second desquamation begins about the time the first one has been finished. The late desquamation on the hands and feet is quite different, and is quite characteristic and rarely entirely absent even in mild cases. It begins on the hands about the end of the third week and is often first detected as a splitting of the epidermis in a line parallel to the free end of the nail. From here it extends over the end of the finger and finally includes the entire palm. The particles of separated epidermis are tough, and in some cases casts of the entire hand may separate in the form of a glove. After desquamation on the hands the skin is red and delicate and devoid of the normal heavy covering. A similar process is usually observed on the feet a week later. Sometimes the feet desquamate earlier than the hands, and one or the other may exhibit typical desquamation while the other is slightly affected. This late desquamation on the hands and feet may be complete in the third or fourth week, but often traces of it are present at the end of fifth or sixth week. Parts covered by heavy callus desquamate very slowly. In infants it is less marked and quickly completed. Cases have been reported in which the hair and nails are shed. This is exceedingly rare, and we have never seen it occur.

In some of the very severe cases in which there is great prostration there is a tendency for the skin to break down at points of pressure, especially back of the elbows and heels and over the sacrum. If pressure is not prevented at such times bed sores are liable to develop and secondary infections may enter.

Sore Throat.—Sore throat is one of the earliest and most constant symptoms in scarlet fever. One sees a bright redness of the pillars of the fauces, velum, uvula and posterior wall of the pharynx. The tonsils are reddened and enlarged. The redness often extends to the roof of the mouth. The reddened tissues are frequently visibly edematous. Small darker spots are often seen upon the soft palate and roof of the mouth which constitute what is sometimes described as the eruption on the mucous membrane. The sore throat is so constant that it is one of the most important diagnostic signs. It was definitely stated to be absent in less than 1 per cent. of McCrae's[78] cases. The degree of involvement of the throat varies much, sometimes consisting only of a punctate blush.

The redness and swelling often extend to the naso-pharynx and nostrils. There is soon an increased secretion of mucous and mucopus from the throat and often from the nose. The patients complain especially of pain on swallowing; and when the swelling is considerable the voice may be nasal, and talking may cause pain. Sometimes, though rarely, the inflammatory process extends to the larynx and trachea, causing hoarseness and cough. Many times there is a follicular exudate on the tonsils, and a delicate grayish-white exudate may be spread over the surface of the enlarged tonsils. The swelling of the tonsils may be so extreme as to displace the uvula forward or backward, the two glands meeting in the center. With these higher degrees of swelling the tissues are very edematous, and the patient hesitates to swallow or expectorate because of severe pain caused by the effort. Pain is often referred to the region of the ear even though there is no appreciable involvement of this organ. The peritonsillar swelling is sometimes more marked on one side, suggesting the beginning of a peritonsillar abscess, and a peritonsillar abscess may form either during the acute disease but more often during defervescence. Infection of a retropharyngeal gland may terminate in suppuration.

Tongue.—The tongue in scarlet fever presents a characteristic appearance in a large proportion of cases. At first it is covered by a heavy white coating, and by the second day enlarging papillæ begin to push themselves through and appear as red dots. Soon the coating begins to desquamate, first at the edges and tip, and by the fourth day the typical strawberry tongue has appeared. It shows a general deep redness with the papillæ enlarged, and often the center is smooth and glazed. The fungiform papillæ are especially large. McCollom[72] placed great stress upon the appearance of the tongue. He said "the most important symptom and the most characteristic feature of the disease is the enlargement of the papillæ at the tip and edges of the tongue; this enlargement may be so slight as to be overlooked, but if a careful examination is made it will be found to be present in every case of scarlet fever." He did not fail to detect it in a single case out of 1000. He described two varieties of enlargement; in one the papillæ look like small grains of cayenne pepper sprinkled on the tongue; in the other the papillæ have a button-like appearance, are considerably elevated, but not specially reddened. Ker[60] also speaks of the "red strawberry" tongue as a practically invariable phenomenon of the fourth day. Most observers would not consider the tongue as characteristic as does McCollom. In other febrile conditions, as measles and diphtheria, the condition of the tongue is not unlike that often seen in scarlet fever when the redness and largeness of the papillæ are not very pronounced.

Mouth.—Except in the very mild cases of scarlet fever the mucous membrane of the cheeks and gums is reddened. Ulcerative stomatitis often occurs, involving the edges of the gums and not infrequently the tongue. These ulcerative lesions on the tongue may be very extensive but are usually quite superficial. They may be very sensitive and interfere with eating.

Esophagus.—Pearce[91] observed ulceration in the upper part of the esophagus in one case and small abscesses in the mucous membrane in another. He refers to a report by Ehrlich of the case of a boy who developed cicatricial stricture of the esophagus three years after scarlet fever with associated severe ulceration in the throat. Ehrlich referred to a single similar case reported by Eiselberg.

Adenopathy.—There is usually a general adenopathy during the acute stage of the disease. The inguinal and axillary glands are usually pea or bean size and firm. Sometimes the inguinal glands are as large as a hickory nut and tender. The cervical glands are usually palpable and may reach the size of a walnut or even of a hen's egg, when they are painful and tender upon pressure.

Temperature.—The temperature varies much in its range and duration according to the severity of the attack and the presence of complications. The initial rise is very abrupt, within a few hours reaching 101 to 105 degrees. It remains at about this level for one to four days with slight morning remissions and then falls gradually by steps for three or four days until normal is reached. Sometimes the fever falls by crisis instead of by lysis. Generally the fever does not abate until the eruption has reached its full development and begun to fade. In a mild epidemic, Welch and Schamberg determined the duration of fever to be from one to 26 days. The largest number of cases were free from fever after six days, and 60 per cent. had fever lasting from five to nine days. Cases with more intense eruptions are apt to develop more fever. Mild cases may show little or no fever. Entirely afebrile attack are very uncommon.

Pulse.—The pulse is more rapid than would be expected from the height of fever, especially in the early part of the disease.

Blood.—The exhaustive study of the blood in a series of cases of scarlet fever by Tileston and Locke[115] lead them to the following conclusions:

1. The blood of scarlatina in children differs from that in adults only in proportion to the differences of normal blood at the different ages.

2. A slight secondary anemia is the rule in all but the very mild cases, varying directly with the severity and duration of the diseases. The fall in hemoglobin is from 5 to 25 per cent. and in erythrocytes from 100,000 to 700,000 per cubic millimeter. Both return to normal after a period of several weeks.

3. A hyperleukocytosis almost invariably accompanies the disease and runs a characteristic course. Rising abruptly in the second to eight day (18,000 to 40,000 per cubic millimeter), the count falls rapidly for a few days then more gradually to reach normal in convalescence, usually at the end of from three to six weeks.

4. During the period of invasion and eruption the polynuclear leukocytes are both relatively and absolutely increased but decrease

rapidly with the fall in the leukocytes till convalescence when they may become relatively, though never absolutely below normal. The mononuclears take an exactly opposite course. With the onset the eosinophiles disappear entirely or are greatly reduced, to rise above normal when defervescence begins. This eosinophilia persists until late convalescence. Myelocytes are often seen in small numbers.

5. Complications, with few exceptions, exert no influence upon the course of the blood. If severe they may increase the anemia and in a few instances even produce a rise in the leukocytes.

These findings correspond very well with those of most observers. As a diagnostic measure the leukocytosis with absolute increase in the polynuclear cells in the earlier stages is of much value. In late cases the high proportion of eosinophiles is also of considerable aid.

Döhle[24] has described certain inclusion bodies in the leukocytes from scarlatinal blood. They occurred early in the disease and were not found after the sixth day. His observations were confirmed by Kretschmer,[70] Nicoll and Williams,[86] and Kolmer.[67] All these authors agree upon the very constant presence of these inclusions in scarlet fever, but they also found them in other diseases with less frequency. Glomset[40] found bodies in the leukocytes in many febrile diseases, in smaller numbers in other diseases and even in health.

Nervous Disturbances.—During the acute course of the disease profound nervous disturbances are not infrequent. There may be a tendency to sleep with a stupor, but often there is active delirium, especially at night, in which the patient wants to get out of bed and is restrained with difficulty. The swelling in the throat and nose with resulting interference to breathing aggravates this and makes the child sit up in bed. Heberden[45] said that "there is no other distemper in which a delirium is of so little importance; in other fevers it seldom comes on till they have arrived at a dangerous height; but it sometimes accompanies a scarlet fever on the very first day, and many of these patients never fail to be light headed every night, though, except this, there be no unfavorable symptoms from the beginning to the end of their illness."

Cases sometimes spoken of as toxic, are characterized by a high fever, very sore throat, painful cervical glands, intense cutaneous eruption including a marked redness of palms and soles, active delirium and a circumcorneal redness of the eyes. This redness of the eyes was noted early by observers and is always an indication of severe intoxication. The redness is due to an injection of the ciliary vessels, and has been described by Huxham[53] as like that due to weeping, and by Withering[125] as like the redness of the eyes of a ferrit. It is not associated with increased secretion. Withering noted that "in proportion to the intensity of this color in the eyes, the tendency to delirium prevails." The tendency to delirium is very strong in scarlet fever during the acute stage. Patients usually answer questions intelligently but when left alone talk incoherently to themselves, and they frequently get out of bed and may wander from their room. Especially in young adults the delirium sometimes resembles that from acute alcoholism. They exhibit a certain cleverness in hiding their mental disturbance when talked to but when left alone again talk to themselves. Such patients may leave their bed and escape from a window, and on two occasions I have known them to get out of bed and go, in one case, to an adjoining room and hide under a bed and, in another case, to a distant room and hide under a table. We have also seen a dementia in two patients during convalescence, terminating in recovery in a few weeks. Tiktin-Hansmann[114] mentions four cases of nervous disturbance after scarlet fever. In three there was evidence of agitation and in one of depression. They all promptly recovered. He refers to about 20 cases in the literature.

Types.—Most writers have classified scarlet fever under several types which are determined by the prominence of certain features. We have been accustomed to group the cases as mild, moderate, toxic and septic. Many cases present a combination of the things characteristic of more than one group.

Mild cases are such as show little fever, mild and transcient eruptions and almost no complications. Occasional instances occur in which no elevation of temperature is ever detected, and others in which no eruption is observed. Doubtless some cases have so transcient eruptions that they are not seen by the physician. If cases could be closely matched at short intervals throughout the attack it is probable that those with no eruption and no fever would be very few. Mild cases also exhibit little desquamation, but most of them show a moderate late peeling on the hands and feet. Even this is sometimes lacking.

Moderate cases are those in which the disease runs its acute course in a few days without complications of any severity. To draw a sharp line between moderate or normal cases which are severe, and toxic cases of a moderate grade is impossible. One class of cases gradually passes into the other, and a separation is arbitrary.

Toxic cases impress one as being under the influence of some virulent toxic agent which exerts its power upon the body as a whole. Such cases vary much in degree. A typical case has a high fever, rapid pulse, intense eruption, often a very painful, red, edematous throat, enlarged and painful cervical lymph-nodes, red eyes, and is often delirious. In extreme cases of this type, designated as "malignant" or "fulminating" and by the French as "foudroyante," the onset is very abrupt with vomiting and often purging, high fever up to 107 to 108 degrees, a pulse of 130 to 160, severe headache, active delirium, slight or severe angina, little eruption and death in 24 hours or less.

In other cases to which the term "hemorrhagic" has been applied, there are added to the toxic symptoms already enumerated a tendency to bleed. The bleeding may occur as epistaxis, hematuria, intestinal hemorrhages, or intra and subcutaneous hemorrhages. Such cases are excessively rare and are sometimes said to have developed a hemorrhagic diathesis.

Septic cases are those in which various suppurative processes play a prominent part. Sore throat is one of the most prominent symptoms in scarlet fever. It is often so severe that it is the only thing of which the patient complains. Much of the fatality from scarlet fever is due to processes which have their origin in the throat. It is not surprising that among early writers, scarlet fever was described by Fothergill[34] under "Sore Throat Attended with Ulcers," by Huxham[53] under "Malignant Ulcerous Sore Throat." by Cullen[19] under "Cyanche Maligna," and by others under "Putrid Sore Throat" and "The Throat Distemper." Cases in which the throat symptoms are specially prominent are often described under "Scarlatina Anginosa, or Septic Scarlet Fever."

The extent and severity of the lesions vary much in individual cases, and reach their greatest development in young children up to five or six years of age. The ulcerative lesions most often involve the tonsils but extend to the pillars, velum, uvula, pharyngeal wall and may include the epiglottis. They are first superficial and covered by a grayish exudate which can only be certainly distinguished from that of diphtheria by bacteriologic examination. If the process extends further, deep ragged ulcers form with friable floors; and sloughing may open vessels with consequent bleeding. Perforations of the soft palate are produced, and parts of the pillars or the uvula may be lost. There is much associated swelling of the tissues in the throat so that the opening of the fauces may be almost closed, and viscid muco-pus is poured out in large amount. An offensive or putrid odor is given off by the decomposing necrotic tissues and secretions. Associated with these conditions in the throat there are often serious disturbances in the ear, mouth and cervical glands. Ulcerations of various forms and sizes, usually superficial, develop upon the sides and upper surface of the tongue. The gums are red and swollen with ulcerations along the border which bleed easily. The teeth may loosen and pus collect about the roots. There is a profuse secretion of saliva. Ulcerative lesions also develop upon the mucous membrane of the cheek and lips. Jochmann[55] saw perforation of the upper lip from such an ulcer. The lips bleed easily and become very sore. There is great senstiveness of the mouth and much pain accompanies efforts to take food or drink.

Extension from the nasopharynx gives rise to purulent rhinitis and sinusitis. An acrid mucopurulent secretion pours from the nose which excoriates the skin of the upper lip, and dermatitis of the cheeks may follow inoculation by the child's fingers when soiled by nasal discharge. The cervical glands are swollen, often to an extreme degree, and spread of the infection beyond the glands to the cellular tissues is followed by a diffuse phlegmon of the neck. The swelling may extend from behind the ears to the mid-line in front and downward to the clavicles and sternum or even beyond.

There is often a suppurative otitis media of one or both sides. Such patients present severe general septic symptoms. There is an irregular fever and rapid pulse with tendency to delirium and much prostration Swallowing and breathing are performed with difficulty and fluids may regurgitate through the nose. In extreme cases these children are most pitiable objects, surrounded by a putrid odor, delirious and resisting every effort at treatment, the head extended that breathing may be less obstructed, the skin of the lip and face excoriated by the profuse purulent discharge from the nose, and pus pouring from the ears. Emaciation may reach an extreme degree.

Surgical Scarlet Fever (Puerperal Scarlatina, Traumatic Scarlet Fever).—Sir James Paget[89] in 1864 called attention to the fact that scarlet fever may occur in surgical patients. Subsequent observers added illustrative examples of the association so that in 1904, Hamilton[44] was able to find 174 instances in the literature not including those of which only passing mention had been made. There has been abundant discussion of the relation of scarlet fever to injuries. Paget inclined to the idea that the wound lowered the natural resistance of the body to infection through the usual avenues. Others have recognized the wound as the break in the defences of the body through which the specific virus of the disease enters. That scarlet fever may occur in persons who are subjects of injuries or operations is evident. It does not appear to have been satisfactorily shown that scarlet fever is more readily contracted by persons with wounds than others. It seems quite possible that the virus of scarlet fever may be introduced into the body through wounds, and it would be proper to limit the term surgical scarlet fever to such instances.

Much confusion has resulted because various rashes, which resemble those of scarlet fever, result from the poisonous action of toxic substances absorbed from wounds. These may be chemical antiseptic agents such as carbolic acid, etc., bacterial poisons, or the products of the decomposition of proteins brought about by bacteria. These latter substances are usually designated septic. The surgical conditions in connection with which scarlet fever has developed are most variable. Of 51 cases reported by Davidovitsch[20] as observed in the Zürich medical clinic during 20 years, 21 followed burns, 11 were during the puerperium, and 19 followed gynecologic and other operations. A number of cases have followed trifling injuries to the hands. Among 2595 cases of scarlet fever in Durand Hospital there were 27 which may be designated "surgical." Six followed operations on the nose, throat and mouth. Two were associated with infected laparotomy wounds. There were slight infected wounds of the hands in six, of the forearm in one, of the feet in two and of the forehead in one. Recent burns were present in two. One followed a bite by a dog. In one there was a recent vaccination. Two occurred in puerperal patients with external laceration. All but three of these cases of scarlet fever developed within a week after the injury. In a large proportion of the cases hemolyzing streptococci were cultivated from the wounds. It is of interest that Tunnicliff[117a] usually found these strains of streptococci to be agglutinated by the serum of rabbits which had been injected with hemolyzing streptococci cultivated from the throat in acute cases of scarlet fever. Aside from a typical cutaneous eruption, each of the cases enumerated had the other signs of scarlet fever including fever, polymorphous leukocytosis, sore throat, and late desquamation on the hands and feet. The case of v. Leube[72] has been of special interest. After frequent exposure to scarlet fever during previous years, he wounded his finger while performing an autopsy on a case of scarlet fever. Seven days later he became ill with fever, vomiting and angina. On the eleventh day a scarlet fever eruption began as a red stripe extending from the injured finger up the arm and then over the body. A similar case was observed in the Durand Hospital during 1913. The patinet was a young physician who had been often exposed to scarlet fever without contracting it. She conducted an autopsy upon a case of scarlet fever while she had a small lacerated wound upon her right index finger. A couple of days later the finger became sore and swollen, and lymphangitis extended from the finger to the elbow. Six days after the autopsy these local disturbances had subsided, when a severe attack of scarlet fever developed with high fever, angina, nausea and diarrhea. A typical scarlet-fever eruption appeared first on the right arm and quickly covered the body. The usual course of scarlet fever followed. A similar case has been reported by Korach.[68]

Guided by our present knowledge of scarlet fever such cases must be recognized as instances of the disease. Any further differentiation and determination of the site of entry of the virus must wait upon the acquisition of knowledge of the essential cause of the disease and of means for recognizing it directly or through specific reactions.

Recurrence.—Recurrence of scarlet fever sometimes occurs during convalescence. Thomas refers to a large number of writers who have reported such cases. It has been usual to separate cases which develop immediately after the initial attack, calling them relapses or recurrences, from those developing within four or five weeks, calling the latter second attacks. Such a separation is necessarily arbitrary and not based on any certain knowledge as to the cause of the fresh outbreak, whether due to infectious material remaining in the body from the original infection or to a new infection from without. It might be desirable to speak of all these cases as recurrent attacks to distinguish from second attacks of scarlet fever which occasionally occur after much longer intervals. Recurrent attacks are not very frequent. McCollom[75] observed 30 examples among 5000 cases or 0.6 per cent. Half of the cases occurred 40 to 50 days after the initial disease began. Klose[64] noted seven recurrences among 856 cases or in 0.8 per cent. They appeared 14, 16, 20, 38, 41, 45, and 49 days after the onset of the initial sickness.

Among 2595 cases in Durand Hospital recurrent attacks occurred in 21 or 0.81 per cent. The intervals between the onset of the primary attack and appearance of the recurrence were 19, 20, 21 (two cases), 24, 25, 27, 28 (two cases), 29, 31 (two cases), 32, 33, 34, 35 (three cases), 36, 40 (two cases) days.

A second recurrence was observed by McCollom[75] in five cases, and Welch and Schamberg[123] also observed one such instance, which they consider vary rare. It is generally said that recurrent attacks are usually milder than the previous ones. This is not always the case. In four of our 11 cases the recurrence was more severe than the primary attack, and once a patient, in whom the primary attack had been very moderate, died during a recurrence. Tiktin and Hansmann[114] observed a fatal recurrence following a mild primary attack. In the recurrent attack the symptoms are those observed in primary ones.

Second attacks of scarlet fever rarely occur. An individual usually remains immune for life after passing through a course of the disease. As in the case of other infections in which one attack confers protection from subsequent ones, the acquired immunity to scarlet fever may occasionally be lost. This has been established by the experience of competent observers.

Complications.—**Cervical Adenitis and Cellulitis.**—Some enlargement of the cervical lymph nodes is so frequent in scarlet fever that it may be said to be a part of the normal picture. In some cases the swelling takes on larger proportions and may terminate in suppuration. The adenitis usually affects the group of glands below the angle of the jaw. As the inflammatory process increases the individual glands are fused in a mass which may reach the size of a hen's egg and may be surrounded by edema of the periglandular tissues. Even at this stage the swelling may subside without suppuration. In Durand Hospital swelling of this grade occurred in 4.9 per cent. of the cases of scarlet fever and subsided without breaking down. The swollen glands are firm and tender upon pressure. The swelling may begin with the sore throat on the first days of the disease, but it reaches its greatest development after the early signs of the disease have disappeared. Severe cases are usually associated with ulcerative lesions in the throat, especially of the tonsils. Elevation of temperature is associated with adenitis, but in many cases it is only one of the symptons of an associated septic process.

Breaking down of the tissues may lead to the formation of an abscess in one or more glands. If this is walled off the suppurative process remains local, and the overlying skin becomes reddened and edematous. Ultimately, pus will escape through the necrotic skin or by perforation into the pharynx. McCollom[77] in 1000 cases of scarlet fever observed suppuration of the cervical glands in 44 or 4.4 per cent. Klose[64] reported it in 5.7 per cent. of his cases.

In Durand Hospital during 10 years, from 1913–1922, in 2595 cases of scarlet fever, cervical abscesses occurred in 47 or 1.8 per cent. In 11, or 23.4 per cent., the right side alone was involved, in 22, or 46.8 per cent., the left alone; and in 14, or 29.8 per cent., both sides. Twenty were in patients below five years of age; 15 between 5 and 10 years; and eight between 10 and 15 years. Thus 74.5 per cent. were in patients aged 10 years or less; and 91.5 per cent. in patients aged 15 years or less. Of the patients with abscess eight died. Thirty-two of the patients, including all with bilated abscesses, were of the septic type. Cervical abscess was more common in the years when the proportion of severe septic cases was greatest.

At times the infection passes beyond the glands, and there results a diffuse phlegmon of the cervical tissues. In this process there may be extensive destruction of tissues, and pus may dissect its way downward to or below the clavicle, sometimes below the pectoral muscle and upward over the side of the head about and above the ear. The large vessels of the neck or their branches may be injured, and perforations may occur with escape of blood, which may either remain enclosed in the abscess cavity or may escape externally through an opening in the skin or through a sinus connecting with the pharynx. More rarely the diffuse phlegmon takes the form spoken of as Ludwig's Angina, in which the tissues have a hard consistence. In this condition the overlying skin is dark red or as it approaches necrosis a pale color. Enormous swelling rounds the neck so that it is even with the jaw, and the swelling extends to the upper chest and onto the face. The eyelids are edematous, and the ears surrounded by the mass of swelling. In this case there is little tendency to localization and abscess formation and necrosis involves isolated areas as occurs in a carbuncle. The interference with breathing is marked, and to relieve the dyspnea the head is thrown back. Such cases are associated with severe symptoms of sepsis and are rapidly fatal. Incision into the involved tissues discloses a diffuse necrosis of all the tissues infiltrated by a serosanguinous fluid, with little or no localized formation of pus and no demarkation of the necrotic from living tissues. Fortunately such cases are very uncommon.

Late swelling of cervical glands may develop in the third or fourth week. There is a slight rise of temperature, but there is little tendency to suppuration. The glands are apt to be very firm and not very tender, and they disappear very gradually, often remaining enlarged for several weeks.

Otitis Media.—Inflammation of the middle ear is a relatively frequent complication of scarlet fever. It is most apt to occur in cases with severe involvement of the throat and is most frequent in the early years of life.

The instances of otitis as they occurred in Durand Hospital during 10 years are collected in Table 6. Otitis media without perforation was noted in 5.3 per cent. of the cases and with perforation in 9.4 per cent. McCrae[78] observed otitis with discharge in 14.7 per cent. of his cases. Klose[64] reported otitis media in 6. per cent. In both McCrae's and Klose's series of cases, the right ear was more often affected. McCollom[75] says that at the South Department of the Boston City Hospital in 5000 cases of scarlet fever, 18 per cent. had middle ear trouble. Wilson[124] observed suppurative otitis media in 100 cases out of 530, i.e., in 18.9 per cent. Jochmann[55] gives the frequency of suppurative otitis in scarlet fever as approximately 20 per cent.

TABLE 6.—OTITIS MEDIA IN SCARLET FEVER IN DURAND HOSPITAL DURING 10 YEARS 1913–1922

Year	Cases of scarlet fever	Without perforation				With perforation				All cases			
		Right	Left	Double	Cases per 100 cases of scarlet fever	Right	Left	Double	Cases per 100 cases of scarlet fever	Right	Left	Double	Cases per 100 cases of scarlet fever
1913	217	4	4	7	6.9	9	5	19	15.2	13	9	26	22.1
1914	193	5	0	7	6.2	5	3	12	10.4	10	3	19	16.6
1915	245	10	7	1	7.3	6	7	7	8.2	16	14	8	15.5
1916	316	8	4	8	6.3	15	8	6	9.2	23	12	14	15.5
1917	284	6	4	10	7.1	10	7	12	10.2	16	11	22	17.3
1918	211	4	4	0	3.6	3	2	7	5.4	7	6	7	9.0
1919	275	4	2	2	2.9	13	4	4	7.6	17	6	6	10.5
1920	340	10	5	4	5.6	12	9	12	9.7	22	14	16	15.3
1921	241	5	1	2	3.3	9	8	4	8.7	14	9	6	12.0
1922	273	6	0	3	3.3	10	12	3	9.2	16	12	6	2.5
Total...............	2595	62	31	44	5.3	92	65	86	9.4	154	96	130	14.6

The frequency of otitis depends largely on the extent and character of the involvement of the throat, and consequently varies much in epidemics. In Durand Hospital from June 16, 1915 to Nov. 25, 1915, 105 cases of scarlet fever were admitted, no one of which developed a discharging ear, but more than 14 per cent. of the cases admitted outside of that period in the same year had this complication. Of 143 cases of otitis media in six years, 8.5 per cent. were in mild cases, 36.4 per cent. in moderate or normal cases, 9.1 per cent. in toxic, and 46.2 per cent. in septic cases. While the largest proportion was in pronounced septic cases, a large part were in moderate ones. It must, however, be noted in this connection that about four times as many cases of moderate type occurred in the series as of the septic type and that the incidence of otitis in septic cases was about five times as great as in normal or moderate ones (Fig. 38).

Age is another element entering largely into the determination of otitis. Figures 36 and 37 covering the experience of 10 years in Durand Hospital, show the proportion of cases of scarlet fever and of cases with otitis and perforation at various ages. It will be noted that otitis with perforation is relatively frequent during the first seven years of life and that it becomes less after this time. Figure 38 shows the proportion of cases of scarlet fever at various ages which developed otitis. Almost 50 per cent. of those between one and two years had discharging ears. With increasing age the proportion fell. It will be noticed that between three and seven years there is a marked irregularity in the curve. The otitis curve has a considerable fall in the three- to four-year period followed by a marked rise in the four- to seven-year period. This occurs in the face of a gradual rise in the number of cases of scarlet fever and of a gradual fall in the proportion of

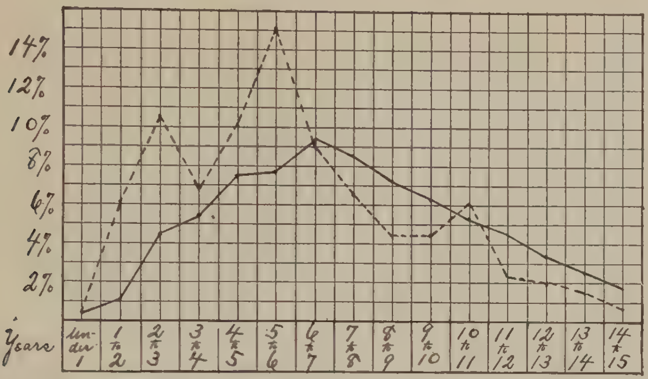

FIG. 36.—Otitis media with perforation in 2595 cases of scarlet fever in Durand Hospital, 1913–1922. Solid line—proportion of cases of scarlet fever at different ages. Dash line—proportion of cases of otitis media with perforation at different ages.

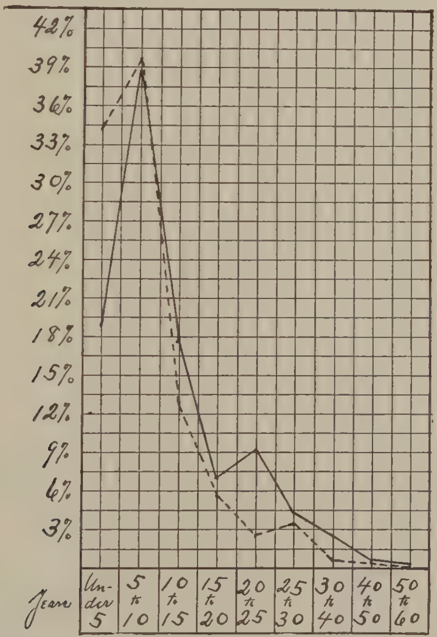

FIG. 37.—Otitis media with perforation in 2595 cases of scarlet fever in Durand Hospital, 1913–1922. Solid line—proportion of cases of scarlet fever in different age periods. Dash line—proportion of cases of otitis media with perforation in various age periods.

septic cases. Whether this would be true in still larger series of cases is uncertain. Between 20 and 25 years the otitis curve falls, although the proportion of cases is higher, but between 25 and 30 years it again rises with a fall in the number of cases of scarlet. We may conclude that the tendency to otitis in scarlet fever is greatest between one and two years, that it grows less with advancing age but that a relatively greater liability is present in the periods between four and seven and between 20 and 25 years.

Otitis media most often develops about the end of the first week but may appear earlier. Occasionally it does not begin until late in convalescence. In young children, especially in those who are very sick, the discharge from the ear may be the first intimation of trouble. In older patients there is pain in the ear with redness and later bulging of the tympanum. It may recede without perforation, or rupture is followed by a discharge. The discharge is first mucopurulent and often blood stained. It becomes more purulent in character, and as the discharge diminishes it again becomes less purulent. In most cases the discharge has ceased and the ear healed by the end of the fourth or fifth week. In patients whose temperatures have become normal or nearly so, the onset of otitis is associated with a rise. With free discharge the temperature falls promptly. When a perforation

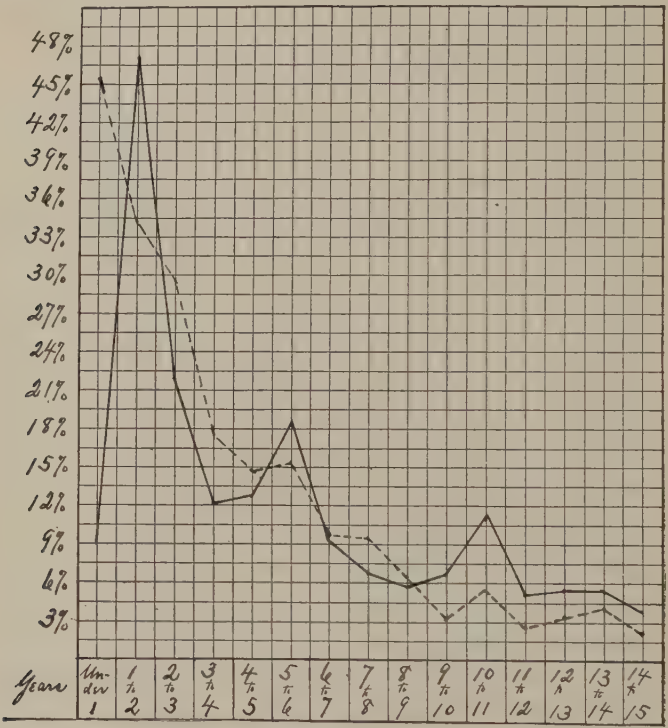

Fig. 38.—Otitis media with perforation in 2595 cases of scarlet fever in Durand Hospital, 1913–1922. Solid line—proportion of cases of different ages which showed the complication. Dash line—proportion of cases of scarlet fever of different ages which were of a septic type.

is small it may close or become occluded, and with the accumulation of secretion the fever may again rise. Hemorrhage from the ear due to injury to the walls of sinuses and other vessels is mentioned elsewhere. Paralysis of the facial nerve may occur during otitis by extension of the inflammatory process to the nerve where it passes through the roof of the cavity. It is often transient. In occasional cases a chronic discharge continues a long time.

Dullness of hearing after recovery is infrequent. However, a considerable number of cases of deaf-mutism are due to damage from scarlet fever. Johannessen[56] quotes Koren who found that 12.58 per cent. of the cases in Norwegian institutions for deaf mutes follow scarlet fever. Bezold[6] studied 233 cases of acquired deaf-mutism 42, or 18 per cent. of which were due to scarlet fever. He calls attention to the fact that in 35 or 83 per cent. of those deaf from scarlet fever extensive destruction of the membrane and often of the ossicles had occurred. The tympanic membrane was almost always intact in deaf-mutism following meningitis. Bezold says that deaf-mutism is acquired in a little more than half the cases. We may, therefore, conclude that about one-tenth of the cases of deaf-mutism follow scarlet fever.

Mastoiditis.—In 2595 cases of scarlet fever in five years in Durand Hospital[30] mastoiditis occurred 28 times or in 1.1 per cent. of the cases. Of 243 cases of otitis media with perforation 28 or 11.5 per cent. developed mastoiditis. Between the ages of one and five there were nine cases; between 5 and 10, 16 cases; between 10 and 15, 3 cases. Fourteen or 96.6 per cent. fell below 15 years. All but three cases, came to operation. Most of the cases with this complication were of a septic type. Streptococcus septicemia, septic thrombosis and thrombophlebitis were not infrequent. Two had an associated purulent arthritis. Meningitis occurred twice. The operated cases had a mortality of 28 per cent. Wilson[124] had eight cases of mastoiditis or 1.6 per cent. among 530 cases of scarlet fever, all of which recovered after operation. Mastoiditis is to be suspected when pain and tenderness develop over or back of the mastoid in patients with an otitis. An elevation of temperature and a leukocytosis are usually associated. Hemolytic streptococci in blood cultures are strongly suggestive of an associated thrombo phlebitis.

Hemorrhages.—Hemorrhages from eroded vessels in the neck, ear, nose and throat are relatively infrequent but usually fatal complications of scarlet fever. These are mentioned by the early writers on this disease. Fothergill[34] states that hemorrhages from the nose and mouth have suddenly carried off patients. Graves[41] says that some died from hemorrhage from the nose, and he also speaks of severe hemorrhages from the ear. Rivers[99] has tabulated 50 cases, comprising most of the authentic ones on record. About 90 per cent. died. The bleeding comes from the nose, throat, ear or an external incision. It occurs when a vessel, whose wall has been weakened by septic infiltration, is opened during the separation of a slough, or bursts when external support is removed in draining an abscess. The affected vessels may be large cervical arteries or veins or any of their branches. In the cases tabulated by Rivers, the arteries and veins were about equally involved. The bleeding usually occurs without warning and a child may be almost exsanguinated before its occurrence is discovered. As the blood pressure falls from hemorrhage, bleeding may cease or be readily controlled by pressure, but as the pressure rises again the hemorrhage is apt to recur. When hemorrhage takes place from the cavity of a cervical abscess it may appear immediately after the incision or, more frequently, after an interval. Rivers has added a case in which repeated severe hemorrhages took place from the cavity of a cervical abscess through an incision made three days previously. The bleeding was from the external carotid artery and internal jugular vein. The common carotid was ligated. Six days later another large hemorrhage took place and was controlled by pressure. Recovery followed.

Haeggström[43] reported a fatal case of scarlet fever in a girl of seven years, in which spontaneous hemorrhage occurred from a mastoid wound as a result of perforation of the wall of the sigmoid sinus. He found 25 similar cases recorded in which osteitis of the sinus led to spontaneous hemorrhage. In five of the ten acute cases, scarlet fever was responsible. A case of this sort recently was observed in Durand Hospital. Repeated profuse hemorrhages from a mastoid wound followed perforation of the sinus wall. In 17 years I have seen two cases in Cook County Hospital and two in Durand Hospital in which profuse hemorrhages occurred from the incisions of cervical abscesses. All were in very septic cases in children of four to five years, occurring two to five days after the incisions were made, and all the patients died. A fourth case in Durand Hospital occurred in a boy of six years with a very septic scarlet fever. A cervical abscess was incised, and two days later profuse hemorrhage occurred from the incision. Packing was followed by cessation of the bleeding, but after a few hours he vomited a considerable quantity of blood and died. The autopsy disclosed a sinus leading from the abscess cavity to the floor of a sloughing ulcer of the pharyngeal wall just below the tonsil. The stomach contained a large amount of blood which had its origin in an eroded vein in the abscess cavity. Bohn[8] has described a similar case. Henoch[48] narrates a case in a child of three years in which an opening from a cervical abscess into the pharynx led to the appearance of blood in the stools. In this case part of the fluid taken by mouth passed through the cutaneous incision.

Nasal Sinusitis.—A purulent inflammation of the accessory nasal sinuses is especially frequent in septic cases of scarlet fever. It is a result of direct extension from the nose. The ethmoid cells are most often affected, and Oppenheimer[87] says that they are affected in practically every instance in contagious diseases of children. Pearce[91] was forcibly impressed by the large proportion of cases with involvement of the sphenoidal sinuses and the antra of Highmore. The most prominent symptom is a profuse purulent nasal discharge, which may be intermittent and sometimes is very persistent. In older patients pain and tenderness occur over the location of the maxillary antrum in the acute stage. Perforation outward from the ethmoid cells may lead to an inflammation and abscess formation in the orbit. Preysing[94] has encountered seven cases in which a suppurative process in the ethmoid cells and frontal sinus perforated into the orbit. The first sign was a swelling of the lids, generally in the inner angle, or a tumor-like swelling at the inner angle. In all his cases the scarlet fever was unusually severe. He says the affection was unilateral in all the cases on record. We have seen this occurrence in two instances. The swelling was firm at first, and later edema was added. In both prompt healing followed incision.

Nephritis.—Nephritis is a relatively frequent complication of scarlet fever. In the early stage of the illness a febrile albuminuria is common and is not be confused with a true nephritis. McCollom[75] reports that in a series of 1000 cases only 28 per cent. failed to show albuminuria. McCrae[78] observed nephritis in 12.5 per cent. of his cases. In a series of cases of scarlet fever extending over 29 years, Klose found nephritis in 13.2 per cent. The proportion varied in different epidemics from 5.3 per cent. in one to 50 per cent. in another.

Among the 2595 cases in Durand Hospital during 10 years, there were 230 or 12.2 per cent. which showed nephritis. In Table 7 we have tabulated our cases according to degrees of severity. It is of interest to note that the cases of nephritis were more abundant in the years when large epidemics of scarlet fever were present in the city. In 1914 and 1917, 12 and 16 cases, respectively, of severe nephritis occurred against two cases in four other years. This variation in the occurrence of nephritis in different epidemics has been described by other writers. Of these 230 cases of nephritis 93, or 3.6 per hundred cases of scarlet fever, developed 14 days or more after the onset of the disease. Thus 60 per cent. of the cases of nephritis occurred in the early part of the disease. Of these early cases only 17 were severe. Three occurred in moderate, eight in toxic and six in septic cases of scarlet fever. Four of the seventeen cases were instances of acute hemorrhagic nephritis. The proportion of cases of nephritis and of severe nephritis which developed in the various weeks of illness is shown in Fig. 39. It will be noted that, while nearly 45 per cent. of all cases appeared during the first week, 57 per cent. of the severe cases developed during the third and fourth weeks. There were 55 cases of severe nephritis. Seventeen of these occurred during the first week and have been referred to above. Ninety-three developed 15 days or more after the onset of illness. The tendency to severe late nephritis would appear to be greatest in septic cases, about equal in mild and moderate cases and least in toxic cases.

The proportion of cases of various ages which developed nephritis and also severe nephritis is shown in Fig. 40. The cases of severe nephritis were fewest between 20 and 25 years of age, and with advancing years the tendency to nephritis increased.

Of the cases of late severe nephritis about 80 per cent. were hemorrhagic. Ten, or about one-third, developed uremia with convulsions.

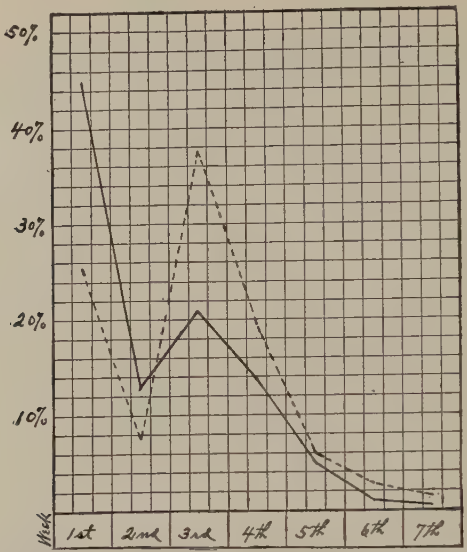

Fig. 39.—Nephritis in 2595 cases of scarlet fever in Durand Hospital, 1913–1922. Solid line—proportion of cases of nephritis developing in various weeks of illness. Dash line—proportion of cases of severe nephritis developing in various weeks of illness.

The cases of scarlet fever in which uremia developed were mild in type in five, moderate in four, toxic in one and septic in one. This

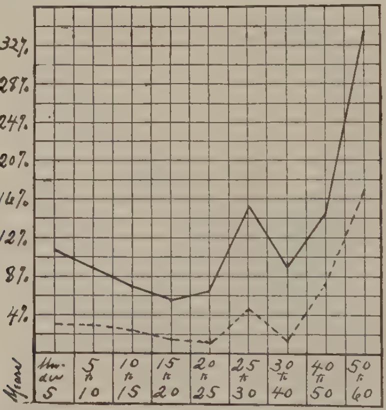

Fig. 40.—Nephritis in 2595 cases of scarlet fever in Durand Hospital, 1913–1922. Solid line—proportion of cases of various ages which developed nephritis. Dash line—proportion of cases of various ages which developed severe nephritis.

bears out the general impression that nephritis with uremia is more apt to occur in the less severe cases and often in the mildest. Klose[64] reported uremia in from 8.3 to 33.3 per cent. of cases of nephritis, the

Table 7.—Nephritis in Scarlet Fever in Durand Hospital during 10 Years, 1913–1922

Years	Scarlet fever			Various degrees of nephritis in cases of scarlet fever																			
				All cases				Mild				Moderate				Severe				Cases developing 14 days or more after onset			
	Cases	Deaths	Deaths per 100 cases	Cases	Deaths	Deaths per 100 cases	Cases per 100 of scarlet	Cases	Deaths	Deaths per 100 cases	Cases per 100 cases of scarlet fever	Cases	Deaths	Deaths per 100 cases	Cases per 100 cases of scarlet fever	Cases.	Deaths	Deaths per 100 cases	Cases per 100 cases of scarlet fever	Cases	Deaths	Deaths per 100 cases	Cases per 100 cases scarlet fever
1913	217	19	8.8	31	6	19.3	14.3	14	4	28.6	6.5	11	2	18.2	5.1	6	0	0.0	2.8	8	0	0.0	4.6
1914	193	14	7.3	41	7	17.1	21.2	22	5	22.7	11.4	7	0	0.0	3.6	12	2	16.7	6.2	15	1	7.1	7.3
1915	245	7	2.9	16	2	12.5	6.5	12	1	8.3	4.9	2	1	50.0	0.8	2	0	0.0	0.8	4	0	0.0	1.6
1916	316	4	1.3	18	1	5.6	5.7	11	1	9.1	3.5	2	0	0.0	0.6	5	0	0.0	1.6	8	0	0.0	2.2
1917	284	12	4.2	43	4	9.3	15.1	21	1	4.8	7.4	6	2	33.3	2.1	16	1	6.3	5.6	17	1	5.6	6.3
1918	211	4	1.9	16	0	0.0	7.6	11	0	0.0	5.0	4	0	0.0	1.8	2	0	0.0	0.9	10	0	0.0	3.6
1919	275	8	2.9	12	1	8.3	4.0	7	0	0.0	2.5	2	0	0.0	0.7	3	1	33.3	1.1	8	1	12.5	2.9
1920	340	6	1.8	13	1	7.7	3.8	5	0	0.0	1.5	6	0	0.0	1.8	2	1	50.0	0.6	8	0	0.0	2.4
1921	241	11	4.5	14	3	21.4	5.8	1	0	0.0	0.4	9	2	22.2	3.7	4	1	25.0	1.7	4	1	25.0	1.7
1922	273	9	3.3	26	3	11.5	9.5	15	0	0.0	5.5	9	2	22.2	3.3	2	1	50.0	0.7	11	0	0.0	4.0
Total.......	2595	94	3.6	230	28	12.2	8.1	119	12	2.5	4.6	58	9	15.5	2.2	55	7	12.7	2.1	93	4	4.3	3.6

variation depending on the epidemic. Efforts have been made by various writers to fix the responsibility for the damage to the kidney upon certain specific factors, such as the essential virus of scarlet fever, streptococcus products, etc. Until we possess more definite information regarding the etiologic agent in scarlet fever, such discussions must be largely hypothetical.

Much difference of opinion has existed among writers as to the part played by diet in regard to the occurrence of nephritis in scarlet fever. Many persons of wide experience have believed that a milk diet reduces nephritis and that more cases occur when a liberal diet including meat is employed. In arriving at any conclusion regarding the part played by diet, it is obviously inaccurate to compare the number of cases of nephritis which develop in different years and epidemics. As a test of the effect of diet, Pospischill and Weiss,[92] over a period of about five years, placed patients into two groups, one of which received milk diet and one meat diet. Each group comprised 1186 children. In one group 9.78 per cent. developed nephritis, in the other 9.95 per cent. The children from 115 families were also placed in opposite groups, and 22.05 per cent. of those on milk diet, and 20.45 per cent. of those on meat diet developed nephritis. Jochmann[55] obtained parallel results in 1000 cases.

"Taking cold" has often been assigned a leading rôle in producing nephritis. Ker[60] relates that no less than 16 of the first 20 scarlet fever patients, in a newly built fever hospital, developed nephritis or albuminuria shortly after they were first allowed to sit up in bed. It was found that ventilating outlets placed above each bed were acting as inlets, and a most perceptible douche of cold air fell upon the backs of the patients. With the closure of the supposed outlets the outbreak of nephritis entirely ceased. Ker[60] also relates that nearly all the children who occupied a certain bed in the old hospital building in Edinburgh developed nephritis. In this case, also, a definite draught concentrated itself on the patient's back. Two of our cases of severe nephritis occurred in children who during convalescence were chilled by getting out of bed and standing at open windows. The nephritis in both appeared immediately after the exposure.

Symptoms of Nephritis.—The cases which appear early in scarlet fever are usually detected in routine urinalyses. The symptoms are not apt to be prominent and are masked by the general symptoms of the disease. The cases which occur later in scarlet fever, usually after the patient has entered upon convalescence, may have a very insidious or a very violent onset. Most often attention is attracted to the condition by a pallor of the skin of the face with puffiness, especially of the eyelids. At the same time the urine is decreased in amount and often is colored red by blood. The edema may be almost entirely confined to the face, but often there is also a swelling of the hands and scrotum and a thick, edematous condition of the abdominal wall. In cases with extreme anasarca, fluid accumulates in the abdominal, pleural and pericardial cavities. To this may be added edema of the lungs and brain. Elevation of temperature often occurs at the onset of nephritis, but the temperature tends to decline as the case progresses.

The urine may at first contain but a trace of albumen, but as it diminishes in quantity the amount of albumen increases and upon heating may become almost solid. In a large proportion of cases blood appears in the urine, rendering it slightly smoky or even brownish-red. The amount of urine is decreased and of high specific gravity. With extensive edema there may be suppression which may persist as long as four or five days in cases which ultimately recover. With abatement of the nephritis the amount of urine increases, and as the edema subsides the specific gravity of the urine falls, remaining at 1004 to 1010 for several days. Microscopically, the sediment contains red blood cells, leukocytes, renal epithelium and casts of various sorts. During the process of recovery it is not infrequent to have recurrences of the albuminuria, and urine which shows no chemical abnormality may contain a few hyaline and granular casts, leukocytes and red blood cells for several weeks or even months. Patients who show no albuminuria while in bed may have it return on arising. Occasional cases occur in which there is a pallor of the face with some puffiness but without anything abnormal in the urine except occasional leukocytes and casts. These patients are anemic and make good recoveries. Uremic symptoms appear in many cases of severe, post-scarlatinal nephritis. They usually develop after other symptoms of the kidney lesion have been present for a few days. Occasionally, uremia may be the first indication of the presence of nephritis. Vomiting and maybe diarrhea are usually the first symptoms of uremia. There is often some fever. Intense headache is common, and the patient often complains of dimness of vision. Convulsions and coma often occur. The convulsions may be universal or limited to parts of the body. They may be single but are often repeated. After severe convulsions coma usually supervenes. Coma may develop without convulsions. Death may result from edema of the lungs, cerebral hemorrhage or from the prolonged intoxication. With the establishment of urinary secretions and decrease of edema the patient emerges from the coma. Localized paralysis may persist for a while, and inability to see may continue for some time but ultimately disappears. Mental disturbances sometimes develop after uremia, taking the form of melancholia or mania.

Permanent damage to the kidney as a sequel of scarlet fever nephritis is infrequent, but well authenticated instances of chronic nephritis as a termination have been reported. Dublin[29] had under observation for an average period of 3.4 years 1063 persons who had recovered from scarlet fever. During this period there were no deaths from kidney diseases. He concludes that among the survivors of scarlet fever the kidneys were not sufficiently impaired to cause early death. McCollom[75] in an analysis of 5000 cases found that chronic nephritis followed in 20 instances. Ker[60] in a large experience saw a single case of chronic nephritis follow scarlet fever. Welch and Schamberg[123] are certain that the number of cases of permanent nephritis following scarlatina has been much underestimated. They believe that many of these patients have structurally damaged kidneys, which at some future time, as a result of a variety of causes, may be reawakened into activity. Among 12 chronic cases of nephritis in children studied by James,[53a] four followed scarlet fever. We have observed a case of acute nephritis following scarlet fever in a girl of eight years. The urine was very slow in clearing up but for many years showed no abnormality upon frequent examinations. About 20 years later she died in her first pregnancy from puerperal eclampsia.

Arthritis.—Arthritis of a non-suppurative character occurs quite frequently in scarlet fever. It is often called "scarlatinal rheumatism" and "serous synovitis." There is much variation in the frequency of its occurrence. In Tiktin-Hansmann's[114] series of 4032 cases of scarlet fever during five years, arthritis occurred in 56 or 4.09 per cent. Brade[9] quotes the statistics of a number of observers among whose cases the proportion of individuals showing arthritis varied from 1.04 to 37.5 per cent. The tendency to arthritis varies much in different epidemics. Brade's figures extend from 1889 to 1903. In these 14 years among 868 cases of scarlet fever 56 examples of this form of arthritis occurred. In the different years the percentage of cases of arthritis varied from 0.0 to 16.4. Klose[64] reported 29 cases among 856 cases of scarlet fever during 29 years. In the first 23 years arthritis occurred only in two out of 556 cases, while in the last six years there were 27 out of 301 cases. The variation in the tendency to arthritis in different epidemics is also shown in the Durand Hospital statistics which appear in Table 8. The cases of arthritis per 100 cases of scarlet fever varied from 3.6 to 17.7, being 10.5 on an average. It will be also noted that the frequency of arthritis was not greatest those years in which scarlet fever was most severe. In fact, in 1916, when the case fatality was only 1.3 per cent., the largest proportion of cases of arthritis developed.

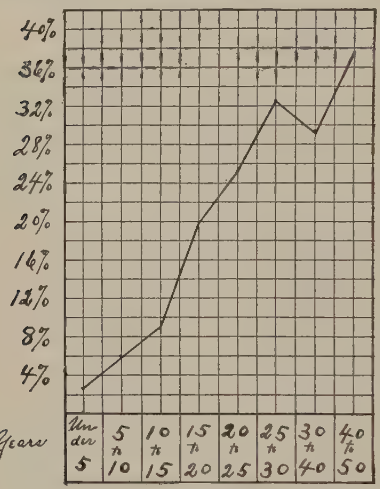

FIG. 41.—Polyarthritis in 2595 cases of scarlet fever in Durand Hospital, 1913–1922. Proportion of patients of various ages showing polyarthritis.

It has generally been remarked that arthritis occurs less frequently in the first decade of life. The increase in the proportion of cases which develop arthritis as age advances is shown in Fig. 41. In the first decade of life 2.19 per cent. developed arthritis, in the second decade 4.57 per cent., and in the third decade 13.33 per cent.

In our series few cases occurred in mild cases of scarlet fever, and they were most frequent and severe in septic cases. Of the cases of severe arthritis 82 per cent. developed in the first week and all in the first and second weeks of the scarlet fever.

A single joint was affected in four cases only. Among Brade's[9] 56 cases one joint was involved in eight, and among Klose's[64] 29 cases a single joint was affected in 14. Occasionally, we have observed a tenosynovitis associated with the arthritis. Koren[69] has observed a muscular involvement, apparently a perimyositis. We have seen an instance of double pleuritis without effusion associated with a polyarthritis in a girl of six years. The small joints in the hands, the elbows, shoulders, knees and feet were involved. Both the joints and pleural conditions entirely disappeared in a few days. The joints most frequently affected are those of the hand, feet and knee. The elbow and shoulder are often attacked. Less often the process involves other joints, scarcely any escaping. Multiple joints may be affected simultaneously, or one may be followed by another.

Table 8.—Polyarthritis in Scarlet Fever in Durand Hospital during 10 Years, 1913–1922

Years	Cases of scarlet fever			Cases of polyarthritis			Cases per 100 cases of scarlet fever
	Cases	Deaths	Deaths per 100 cases	Cases	Cases per 100 cases of scarlet fever	Severe cases	
1913	217	19	8.8	22	10.1	7	3.2
1914	193	14	7.3	24	12.4	7	3.6
1915	245	7	2.9	15	6.1	5	2.0
1916	316	4	1.3	56	17.7	15	4.7
1917	284	12	4.2	37	13.0	5	1.8
1918	211	4	1.9	8	3.6	0	0.0
1919	275	8	2.9	13	4.7	2	0.7
1920	340	6	1.8	40	11.8	17	5.0
1921	241	11	4.5	21	8.7	8	3.3
1922	273	9	3.3	37	13.6	13	4.8
Total............	2595	94	3.6	273	10.5	79	3.1

The joints are stiff, painful on motion, and there is often moderate swelling and redness of the overlying skin. Many exhibit no swelling or redness. Moderate fever of an irregular type is often associated but may be absent. The affection is usually transient lasting three to five days but may continue one to two weeks or more. Persons who have had rheumatism previously are especially apt to be affected by arthritis during scarlet fever, and in such persons it is often more persistent. Blood cultures made in a series of our cases were always sterile. There is no associated endocarditis as in acute rheumatism, with which this form of arthritis seems to bear no relationship. Klose[64] twice observed tuberculosis of joints following scarlet fever. Fritsch[37] speaks of cases which became chronic and terminated in luxations and subluxations from distension with fluid or in stiffness and limitation of motion from hyperplastic deposits.

Purulent arthritis is fortunately a rare complication of scarlet fever. Brade's[9] 868 cases of scarlet fever showed four instances of suppurative arthritis, two of single and two of multiple joints. Three of the cases were fatal. Klose's[64] 856 cases included only one. The left knee and elbow were involved, and the case ended fatally. Fritsch[37] concludes from a study of statistics that purulent arthritis appears in about 0.11 per cent. of cases. In 2595 cases in Durand Hospital four examples of purulent arthritis occurred, three of which terminated in death. All the cases were of a very septic type, and other septic processes were associated with the arthritis. In the fatal cases the joints affected were both elbows in one, both knees and an elbow in another, and the hip joint in a third. The case which recovered was in a boy of five years in whom one elbow was affected. Drainage and healing were followed by little limitation of motion. The infection was caused by a hemolyzing streptococcus. In all of Brade's cases streptococci were found in the pus. Edgerly[31] reported a case of purulent arthritis of the hip joint following scarlet fever in a child 6½ years old. Drainage of a peri-articular abscess and later excision of the neck of the femur was followed by healing with a serviceable but shortened leg. In this case, also, streptococci were cultivated from the pus.

Purulent arthritis usually develops later in the disease than does the simple arthritis and is confined to one or two joints. It occurs in cases with other septic complications, especially ulcerative angina. The cases are in children less than 10 years of age, and it is likely that the infection sometimes first locates in the epiphyses of bones rather than primarily in the serous structures. There is swelling of the joint which is very painful, and the overlying skin is red. General symptoms of a septic character, including an irregular fever, are present.

Purulent bursitis was observed in our series of 2595 cases three times. Twice it involved the burse over the olecranon, in one instance bilaterally. In the other case it was beneath the deltoid posteriorly on both sides. All the cases were very septic. Pressure seemed to determine the localization of the infecting streptococci which were present in the pus.

Myocarditis.—Changes in the heart muscle are frequent in scarlet fever. Pearce[91] observed fatty degeneration of the muscle in about five out of nine cases examined, and he frequently noted myocardial fragmentation. Stegemann[109a] made a thorough study of the heart structures in 49 fatal cases of scarlet fever. In cases of the severe toxic type with early death, the changes noted were mostly in the heart ganglia. In cases of longer duration he found acute parenchymatous degeneration, fatty degeneration and necrosis, and infiltration with round cells. Probably because of these alterations in the heart muscle cardiac dilatation with resulting murmurs are not infrequent. They occur sometimes in mild cases but more often in the severe ones and are especially apt to appear during a nephritis. These functional murmurs disappear as the muscle tone is regained. McCollom[75] observed cardiac murmurs and irregularities of rhythm in 18 per cent. to almost 50 per cent. in three series of 1000 cases each. Rosenbaum[99a] reported myocardial complications in 88 out of 1770 cases of scarlet fever. In 53 it was mild, in 31 moderately severe, and in five very severe. He notes that myocarditis is most common in the latter days of the acute stage or in early convalescence. During the fourth and fifth weeks slight irregularity of the heart not infrequently appears without other symptoms and disappears in a few days without other treatment than quiet in bed. Sudden death during the second or third week of scarlet without previous symptoms may be due to cardiac dilatation. Among 2322 cases of scarlet fever, Krauss[69a] records the occurrence of sudden death in two patients, 23 and 34 years of age. In one which came to autopsy the heart muscle was extensively degenerated. Weill and Mouriquand[121] report sudden death in a girl of 15 years, who had recovered from a mild attack of scarlet fever.

Endocarditis has often been spoken of as a common occurrence in scarlet fever, probably because of the frequent functional murmurs at the apex and because it was natural to associate an endocarditis with the frequent arthritis, inferring that the condition was related in some way with articular rheumatism. There does not appear to be any tendency to endocarditis in the cases with arthritis, and endocarditis is uncommon in scarlet fever. Pearce[91] mentions endocarditis in the anatomic diagnosis but once in his series of 23 autopsies. Pospischill and Weiss[92] say that out of a very large amount of material, an endocarditis appears on the autopsy table only at long intervals.

In Rosenbaum's series of 1770 cases of scarlet fever endocarditis was present in four. Two of the patients died.

Pericarditis of a purulent nature occurrs in septic cases of scarlet fever and is usually associated with other serous involvements.

Skin Complications.—In cases with excessive secretion from the nose the skin of the upper lip and cheek often is the seat of a dermatitis. A similar condition is also produced by the discharge from the ear upon the skin over which it flows. In cases with diarrhea the skin of the buttocks is also often excoriated. Secondary pus infections in the form of boils occur, especially in weakly children during convalescence. These may be very persistent and troublesome and not infrequently are located in the scalp. Because of the common habit of children of putting the fingers in the mouth and nose, slight cutaneous defects at the edge of the nails often become infected and paronychia result. These defects may result from forcibly pulling away tough fragments of epidermis which have only partly separated.

Herpes is quiet frequent in scarlet fever. Among our 2595 cases, herpes labialis was observed in 47. Herpes sometimes appears also on the cheek. In one case we saw herpes of the chest and abdominal wall on one side, and in one case in a boy of four years, typical herpes zoster occurred during convalescence.

Eye Complications.—Occasionally infection extends to the lachrymal sac and a dacryocystitis results. With occlusion of the duct the gland may be distended and suppuration of the periglandular tissue with an abscess result. Tito di Giuseppe[23] observed many eye complications in an extensive epidemic of scarlet fever. There were four cases of corneal ulcer, two of iritis and four of panophthalmitis. We have seen one case of corneal ulcer with associated hemolyzing streptococci, which terminated in panophthalmitis and loss of the eye. We have already referred to extension of inflammation from the accessory sinuses to the orbit.

Gangrenous processes occasionally occur during the course of scarlet fever. A few cases have been reported in which gangrene of the legs was apparently due to embolism and thrombosis of principal vessels. Symmetrical gangrene of the skin occasionally is observed. In the hospital of the John McCormick Institute for Infectious Diseases in 1903 such a case occurred in a girl of 2⅓ years. On the thirteenth day after the onset of scarlet fever, superficial areas of gangrene appeared over the flexor surface of both elbows and at the sides of the ankles. A similar small area was located upon the abdominal wall. The case had various septic complications and died a week after the gangrene began. The form of gangrene, known as noma, which involves the mucous membrane, skin and intervening tissues in the neighborhood of the orifices of the body and affects most often the face but sometimes the vulva, occurs in scarlet fever in rare instances. Tourdes[116] collected 98 cases of noma from the literature, 47 of which complicated eruptive fevers. Of the 47, five were observed in cases of scarlet fever. Woronichin[126] reported four cases in scarlet fever out of 22 instances. A case associated with scarlet fever was reported by Weaver and Tunnicliff[119] in 1907.

Appendicitis.—Among our patients four developed acute appendicitis during the course of scarlet fever. In three the attack was primary; in one numerous previous attacks had occurred. All recovered without operation. The patients were 9, 10, 21 and 22 years of age. Kauffmann[58] called attention to the frequency of changes in the lymphoid tissues of the appendix. These alterations may predispose to acute inflammatory changes.

Diphtheria.—Diphtheria may occur in persons with scarlet fever. It also happens that carriers of diphtheria bacilli contract scarlet fever. The frequency with which the secondary infection with diphtheria occurs will depend largely on the prevalence of the bacilli in a community. At time when diphtheria is especially wide spread more instances of the secondary infection occur. In 1907, Ker[60] observed concurrent diphtheria in 20 patients out of 1039 admitted to the Edinburgh City Hospital with scarlet fever, i.e., in nearly 2 per cent Among 2595 cases of scarlet fever admitted to Durand Hospital in 10 years there were 69, or 2.7 per cent., with diphtheria bacilli in cultures from the throat and nose. In Blatt's[7] report of 115 cases of scarlet fever with diphtheria, 31, or 27, per cent. died. McCrae[78] found diphtheria bacilli in the throat on admission in 82 or nearly 10 per cent. of 850 cases of scarlet fever. Welch and Schamberg[123] obtained diphtheria bacilli in cultures in 285 or 29.25 per cent. of 1259 cases of scarlet fever. Such reports would indicate that diphtheria is a more or less frequent complication of scarlet fever and that the statement of McCrae that "scarlet fever and diphtheria are deadly diseases, and the combination is more powerful than the added strength of the two is true. Zingher[128] has shown that children with scarlet fever are about twice as susceptible to diphtheria as normal children. About 65 per cent. of children with scarlet fever between two and four years of age gave positive reactions with the Schick test as compared with about 32 per cent. in normal children. Because of the common occurrence of pseudo-membranous exudates in scarlet fever, a certain diagnosis of diphtheria in these cases is only possible by means of carefully made cultures.

Diagnosis.—Typical cases of scarlet fever are usually recognized without difficulty. The leading features are sudden onset with vomiting, sore throat, punctate eruption on soft palate, eruption beginning on chest and extending over the body and moderate leukocytosis. Later in the disease aid is given by a rise in the blood of eosinophiles, strawberry tongue, peeling of the hands and feet and enlarged cervical glands. The tongue is often not characteristic and especially in the early stage may not differ perceptibly from that of diphtheria, measles, etc. Desquamation is not to be entirely relied upon as it may follow erythema from other causes. Any severe congestion of the skin may be followed by desquamation. The late peeling upon the fingers is, however, quite characteristic of scarlet fever and rarely occurs in other conditions. Some peeling of the hands and especially of the feet occurs in patients who have been confined to bed for any reason. The presence of Doehle's inclusion bodies in the leukocytes possesses no positive value as they also occur in other diseases, but their absence speaks against scarlet fever since they are so constantly present in this disease.

Measles is not apt to be confused with scarlet fever. The presence Koplik's spots in the mouth, later the velvety roughness of the mucous membrane of the cheeks, the more marked catarrhal symptoms and the typical leukocyte picture usually make a differentiation quite easy. Even when the measles rash is confluent patches of normal skin can be seen, and the color of the eruption is a deeper red. Little rash is seen on the face in scarlet fever while in measles it is apt to be very prominent. In some cases of scarlet fever, especially of the toxic type in which the general eruption is transient or absent and in which a patchy eruption persists, measles must be excluded by other points of difference.

German measles is sometimes distinguished from scarlet fever with difficulty. At the beginning of an epidemic, especially, cases are liable to pass as scarlet fever. The eruption at first consists of indistinct spots on the face and body. Angina is less prominent. There is little or no fever, and the typical blood picture of scarlet fever is absent. The prominent postauricular glands are absent in scarlet fever.

Acute exfoliative dermatitis is characterized by severe itching, marked desquamation and a tendency to relapse. The eruption is often intense, and desquamation begins early even before the eruption fades and is often most profuse. The nails and even the hair may be lost.

Serum rashes are sometimes very confusing. The occurrence 8 to 12 days after the administration of serum is always suggestive. Often the rash begins at the point of injection and extends from there over the body. There may be associated urticarial lesions. As a leukocytosis may be produced by the condition for which the serum has been given, the leukocyte picture may not aid in the differentiation. The absence of a leukocytosis would speak against scarlet fever. Special difficulty occurs when the scarlatinal form of the serum rash follows the administration of serum in diphtheria if the sore throat and leukocytosis of the diphtheria are still present.

Toxic erythemas are often very puzzling. They may follow the use of enemas, the administration of drugs such as quinine, belladonna, antipyrin, aspirin, arsenical preparations,etc. The fever, sore throat and leukocytosis of scarlet fever are lacking. Erythemas associated with gastro-intestinal disturbances in small children are sometimes very difficult to differentiate from scarlet fever as the illness may begin with vomiting and have an associated fever.

Prodromal erythemas with the onset of various diseases may be mistaken for scarlet fever. Such erythemas occur in small-pox, chicken-pox, measles, pneumonia, typhoid fever and influenza. Hektoen,[47] in making routine blood cultures from cases of scarlet fever, secured pure growths of typhoid bacilli from two patients who had been admitted with a diagnosis of scarlet fever. During five years in Durand Hospital a similar occurrence happened twice. Young children with lobar pneumonia occasionally enter hospitals as cases of scarlet fever because of an erythema of the skin, especially prominent over the chest. The further course of the disease usually quickly clears up the diagnosis in these cases. Usually, the characteristic signs of scarlet fever are absent.

Sometimes cases of scarlet fever in small children are mild at the onset, and any eruption is overlooked. Later they take on a septic character with severe naso-pharyngeal and glandular involvement and are apt to be mistaken for diphtheria. The final exclusion of diphtheria in such cases depends on bacteriologic examination.

Prognosis.—The death-rate in scarlet fever varies greatly in different epidemics. The fatality in different types has been already discussed. While most of the mild and a large proportion of the moderate cases recover completely, the possibility of severe and even mortal complications must not be forgotten. It is unsafe to certainly predict that no further complications will occur until recovery has begun and five weeks have past. If the structures in the throat at the beginning of the attack are in good condition the outlook is more favorable. Chronically enlarged tonsils and adenoids always add to the dangers of glandular, ear and sinus complications and render the prognosis less favorable. While there is any inflammatory condition in the middle ear the possibility of mastoid extension must be borne in mind. Cases of nephritis tend to recover. Some are prolonged, and a few may become chronic. Rosenfeld and Rechtenstamm[100] followed for several years 93 persons who had nephritis in connection with scarlet fever. No case developed severe chronic nephritis. Even when uremia develops a large proportion get well, but death may occur during convulsions or in coma after several days. In septic cases the prognosis must always be uncertain. Purulent pleurisy and pericarditis due to streptococci are very fatal, and only a bad prognosis can be given in such cases. Bronchopneumonia in small children is often fatal. In very toxic, fulminating cases the outlook is almost absolutely bad. A tendency to bleed with the development of what has been spoken of as a "hemorrhagic diathesis" usually points to a fatal termination. When diphtheria complicates scarlet fever it adds considerably to the gravity of the disease and renders recovery less likely. While hearing is not often appreciably affected after recovery from scarlet fever otitis, sometimes dullness of hearing persists and occasionally total deafness ensues.

Treatment.—In 1748 Fothergill,[34] speaking of the treatment of scarlet fever, said that "in some cases this disease appears to be of so mild a nature and so benign as to require but little assistance from art; persons even recover from it under the disadvantage of unskilled and injurious management; whilst in others, the progress of the symptoms is so rapid and the tendency to corruption so strong that nothing seems able to oppose it." Again in 1781 he outlines the treatment as follows: "Free, but not cold air, plenty of liquid nutriment and generous, with constant attention to keep the patients clean, their mouths and throats washed, and their linen changed, contribute greatly to the cure of the disease."

About a century later Gregory,[42] in 1843, said: "We are not ashamed to acknowledge that many diseases *must* run their course, and that others will run their course in defiance of all the efforts of medical skill. In the management of the exanthamata, be satisfied with steering the ship. Do not attempt to quell the storm." Nearly three-quarters of a century later, Osler[88] in 1905 speaking of the same subject says: "The disease cannot be cut short. In the presence of the severe forms we are still too often helpless," but he adds: "There is no disease, however, in which the successful issue and the avoidance of complications depends more upon the skillful judgment of the physician and the care with which his instructions are carried out." We must acknowledge that the statements of these early English writers on scarlet fever still hold true, and the treatment outlined by Fothergill still comprises all that we consider most essential in the routine management of a person sick with scarlet fever. We must also insist with Osler that very much can be done by medical and nursing care which will limit the damage suffered by the patient and which will sometimes determine the outcome of the sickness.

It will be convenient to consider the management of scarlet fever under three heads:

1. Prophylactic measures.
2. Treatment of the usual case.
3. Treatment of cases with special complications.

Prophylaxis.—Measures should be instituted to prevent infection with scarlet fever. It is especially important that the young children should be protected from the disease. Gabritschewsky[38] in 1905 introduced the injection of devitalized streptococci which had been cultivated from cases of scarlet fever as a prophylactic measure. While favorable reports came from Russia as to the value of this practice, it has not been favorably received elsewhere. A resume of the most important publications upon this procedure has been prepared by Smith.[76] In the absence of any accepted means of specific protection general measures must be emphasized. When possible young children should be removed from a house in which a case of scarlet fever develops and placed away from other children during the incubation period. The removal of adenoids and diseased tonsils from all children will do much to moderate the disease if it should occur.

Isolation of the patient is the most important available measure in preventing the spread of the disease. When conditions are favorable this may be done at home. There must be available a room which will not be entered by any except the attendant and which does not communicate freely with other parts of the house. It must be screened to exclude flies and other insects. To facilitate proper cleaning of the room at the termination of the illness, all unnecessary furniture, pictures, rugs, draperies, etc., should be removed before the patient is placed in it.

If proper isolation cannot be secured at home the patient must be removed to a hospital. Here those who are very sick and especially those with septic complications should be kept apart from uncomplicated cases in order to prevent secondary infections. General hospitalization of scarlet fever does not appear to appreciably affect its prevalence in a community. In England, where efforts to control scarlet fever by hospitalization of all cases have been carried out most thoroughly, it has apparently failed to accomplish the desired result. Districts in which hospitalization has been most complete often have continued to have more scarlet fever than other districts in which hospitalization has been very limited. Chapin[12] also points out numerous instances of the inefficiency of isolation in American cities and directs attention to the fact that cities with inferior sanitary administrations often have less scarlet fever than those with the best sanitary administration.

Only the person acting as nurse should enter the room. When entering the room the attendant should cover the clothing completely with a gown. This should close well about the neck. The hair should be covered by a linen cap. These are removed when leaving the room, gown being hung up with the outside turned in. Duplicate gown and caps should allow frequent disinfection by boiling. Nothing is to be taken from the room unless it is previously or immediately sterilized. Toys, books, etc., should be kept in the room until the termination of the isolation and then burned. Eating utensils must be boiled in water when taken from the room. All bed and other linen should be boiled before washing. Pieces of gauze or old linen are to be substituted for handkerchiefs, and they are to be used for collecting all discharges and then burned. It is convenient to collect such pieces of gauze and other small soiled articles in a paper bag which can be burned with its contents. Experience indicates that there need be but little use of antiseptics. After handling the patient and before leaving the room the attendant thoroughly washes the hands with soap and warm running water. It is important that the attendant should appreciate that the spread of the disease is through the discharges from the throat, nose, ears, etc., and that every effort should be directed toward their destruction and the prevention of their dissemination.

There is every reason for believing that the old theory of aerial dissemination at distances should be abandoned. The sheet wet with an antiseptic solution and hung over the door of the room only serves the harmful purpose of distracting attention from vital things. It probably has no more value than a board placed over the chimney of the house to protect passers-by, which measure the writer saw used not many years ago in an intelligent college city.

The time during which a quarantine should be continued has to be determined in an arbitrary manner. Experience indicates that five to six weeks is a sufficient time if the patient has no abnormal conditions remaining in the nose, throat, ears, etc. Late roughness of the hands and feet do not seem to be of any danger. In any case if enlarged inflamed tonsils, a nasal or aural discharge, a discharging wound from a mastoid operation or suppurating cervical glands persist, isolation must not be terminated. Abundant evidence indicates the danger of infection from such conditions. When the patient is released from quarantine, the entire body is to be thoroughly cleansed with soap and warm water. This must include a careful washing of the hair. Outside the room the patient is given clean clothing. A similar cleansing is carried out for the attendant.

After evacuation the room is carefully cleaned. Sunshine and free air do more than volatile antiseptics in destroying infectious materials. The tendency is to use less fumigation and more soap and water. Thorough washing with warm water and soap of everything which can be so treated is carried out. This includes the floor, windows, and doors. Previously, the linen has been all removed, immersed in water and boiled before washing. Blankets and covers should be thoroughly aired in the sun several days. If the mattress has been soiled it is best burned. If not, it is aired in the sun very thoroughly. Blankets and covers, if soiled, must be also boiled or burned. A fresh painting and papering of the room is desirable. A thorough cleaning as outlined is considerably more valuable than fumigation as usually carried out. Fumigation not only fails to accomplish what it is designed to do, but it also gives a feeling of false security which is apt to lead to a neglect of proper and efficient cleaning.

Management of the Usual Case.—All cases of scarlet fever should be put to bed in a well-ventilated room, preferably one which receives sunlight part of the day. The duration of the stay in bed may vary, but it is probably best to insist on its continuance in all cases for three weeks. Small children are liable to chilling when allowed on the floor, and they are best kept in bed for four weeks. After the acute stage has passed patients may be allowed to sit up in bed. Water is to be given freely, and fruit juices may be added to it. Weak tea is often an acceptable drink to those accustomed to it. The diet during the febrile period should be milk with gradual addition of cereals, vegetables, fruits and bread as the appetite indicates. Later eggs may be added, and meat may be allowed after the third week. Daily baths should be given, and during desquamation the bath may be followed by inunction with some bland oil. Benzoinated lard is very good for this purpose. The patient must be carefully protected from chilling of the skin. The bowels should be regulated, and a daily enema or mild laxative administered when needed. The mouth should be kept clean, and in persons old enough to use them mild gargles should be used several times a day. If the throat is very sore or there is swelling and tenderness of the cervical glands, the application of ice bags to the neck gives much relief.

The urine must be examined frequently throughout the febrile period and during the third and fourth weeks. A culture from the throat for diphtheria bacilli should be made in each case at the beginning and in any case with a very sore or suspicious throat this precaution is well repeated. In some hospitals it has been customary to administer an immunizing dose of antitoxin to all cases of scarlet fever at the time of admission. This is specially to be advised where facilities for the isolation of the individuals is limited.

Management of Cases with Complications.—Most of the complications developing in scarlet fever are treated in the same way as they occur in other connections. It is, however, desirable to consider the management of some of the more frequent complications, as they occur in scarlet fever with certain peculiarities.

The treatment here given for otitis media is that outlined by Friedberg.[36] When pain is present in the ear, a few drops of warm glycerine containing 10 per cent. of carbolic acid are dropped into the ear and heat applied. If the tympanum becomes red and bulging paracentesis is performed. This may have to be repeated. When there is profuse discharge from the ear gentle irrigations are used to wash away the discharge. The canal is then dried with small swabs of absorbent cotton and a gauze wick inserted to the bottom of the canal. As the discharge becomes scanty, cleansing with saturated solutions of boric acid in alcohol of graduated strengths is substituted for the irrigations. As the gauze wicks become soiled they are replaced by fresh ones. An effort is made to keep the ear as dry as possible. Usually, the ear becomes free from discharge in three to four weeks. Cases which become chronic require special measures.

In our experience mastoiditis in cases of scarlet fever produces rapid and early destruction of bone and frequent involvement of the sinus with thrombosis and septicemia. Most of these cases come to operation; and it must not be long delayed.

Purulent nasal sinusitis is often very persistent and may become chronic. In the acute stage drainage is facilitated by the use of adrenalin solution followed by an alkaline spray. A few drops of petrolatum containing a little camphor and menthol, as recommended by Friedberg,[36] reduces the swelling and facilitates the passage of air through the nose. Where the discharges irritate the lining of the nose and produce superficial abrasions, a 2 per cent. solution of argyrol is often beneficial.

Cervical Adenitis and Cellulitis.—Ice bags are applied to the neck when the cervical glands are swollen and painful. For this purpose we have found pigs' bladders preferable to rubber bags. They are light, very pliable and so inexpensive that new ones can be used in each case. As soon as pus is detected it is evacuated. It is not best to incise swollen glands until pus is well localized. Incisions made before this open up new opportunities for infection and accomplish no good end. It is surprising how often glands which seem on the verge of suppuration will resolve without breaking down. When there is extensive phlegmonous infiltration of the tissues of the neck free incisions seem indicated but rarely appear to give much relief.

Nephritis.—When nephritis appears the patient must be kept warm in bed, the bowels kept active and the diet limited to milk. Moderate cases usually clear up under such management. If the case becomes severe with edema of the face and scanty, bloody urine, fluids should be restricted, free catharsis secured and sweating induced. Sweating in children is usually produced by placing them in a hot bath until sweating begins. They are then wrapped in a blanket, and sweating is allowed to continue 20 minutes to half an hour. During all this time cold is applied to the head. It may become necessary to discontinue the sweat at any stage because of a bad pulse, which must be carefully watched. Salt is removed from the diet, and cream substituted for milk. It is customary to administer alkalis in moderate amount. Sodium bicarbonate and citrate in doses of 20 gr. are given every four hours. When the blood tension is low digitalis acts beneficially. As the secretion of urine begins to increase and the edema grows less, fluids are increased. When convulsions occur, catharsis and sweating are pushed further. Venesection often seems of value. Lumbar puncture appears to have a distinct value in checking convulsions. Of sedatives, morphine hypodermically is most prompt and apparently most reliable. As the edema subsides Basham's mixture is useful. After the kidney secretion is well established, patients are usually anemic, and the diet must not be too long restricted. The last of a nephritis often disappears best under liberal feeding.

Arthritis.—The arthritis which complicates scarlet fever tends to recovery in a few days. Some relief of the pain is afforded by the moderate counter-irritation produced by friction with oil of wintergreen and by the warmth of a covering of cotton or flannel. The pain, also, is sometimes relieved by antirheumatic remedies.

Diphtheria.—When diphtheria complicates scarlet fever it adds so much to the gravity of the condition that it calls for vigorous treatment with antitoxin. In cases which resemble diphtheria clinically antitoxin must be given without waiting for the results of cultures.

Purulent arthritis and empyema call for surgical measures. In both the outlook for cure is not promising. Peritonsillar abscess and retropharyngeal abscess both require incision.

Many cases of scarlet fever call for remedies to counteract the anemia which is frequent during convalescence, especially after cases of the septic type. In cases of otitis and nasal sinusitis which become chronic, distinct benefit sometimes appears to be derived from the administration of Syr. ferri iodidi. For the severe ulcerative angina in persons old enough to gargle, benefit is derived from gargling with diluted peroxide of hydrogen. Another gargle which often does good is that of dilute Tr. ferri chloridi, as was formerly used so largely in the local treatment of diphtheria.

Specific Therapy.—The very frequent association of streptococci with scarlet fever and its complications has led to efforts to oppose them in a specific manner. In these procedures streptococci have been considered the cause of scarlet fever by some and secondary invaders by others.

Streptococcus vaccins have been used to combat infections already present and to prevent secondary infections expected to occur later. In both instances the results have been disappointing. Streptococcus vaccins seem to possess some value in chronic infections following scarlet fever but do not exert much influence in preventing streptococcus complications during the acute course of the disease.

Anti-streptococcus serum prepared from strains isolated from scarlet fever has been employed on a large scale in treating scarlet fever. Baginsky[1] was, at first, favorably impressed by results following the use of serum but later abandoned it because of its slight or questionable value. Moser[82] made special claims for his anti-streptococcus serum in treating scarlet fever, and there were numerous favorable reports from enthusiastic users, but it also has not stood a general test. Properly prepared anti-streptococcus serums contain specific antibodies for streptococci. The great drawback to their therapeutic use is the fact that the antibodies are in such low concentration that very large doses of serum are demanded to produce any possible effect. In such doses as 100 to 200 c.c. the foreign serum is itself harmful and this may more than offset any good effects from its antibody content.

In view of the fact that specific antibodies appear in the blood during the course of many infections it would naturally be expected that this might occur during the course of scarlet fever. Upon this assumption the serum of patients convalescent from scarlet fever has been used in the treatment of persons acutely sick with the disease. This was practiced by Weisbecker[122] in 1897 and during the following six years by Huber and Blumenthal,[52] Von Leyden,[73] Rumpel,[102] and Scholz.[104] Together they treated 69 cases by injecting subcutaneously 20 to 40 c.c. of convalescent serum. Their results were very indefinite. In consideration of this result and the fear of transferring syphilis, the method of treatment was abandoned. When syphilis in the donor of the serum could be excluded by the Wassermann test and when experience had been acquired in administering larger amounts of serum intravenously and intramuscularly, the treatment of scarlet fever with convalescent serum was revived by Reiss and Jungmann[98] in 1912. They together with Koch,[65] and Reiss and Hertz[97] treated a considerable number of cases of severe scarlet fever with convalescent serum in doses of 40 to 100 c.c. administered intravenously. The serum appeared beneficial. In 1915, Zingher[127] reported the treatment of early toxic or malignant cases of scarlet fever with the blood of convalescent patients injected intramuscularly. Kling and Widfelt[63] have reported most favorable results from the use of convalescent serum in a large series of cases. They found it specially useful in serious toxic cases with comparatively little influence in warding off or curing complications. In 1918 the writer[118] reported 19 cases of scarlet fever which had received injections of convalescent serum. In 1921[118b] 35 additional cases were added. Before Jan. 1, 1924, 98 patients with scarlet fever in Durand Hospital were treated by injection of convalescent serum. The very sick patients only were given serum. Of these five died. Of the 98 cases, 71 were of the toxic type, 27 had septic complications. Of the fatal cases, three were profoundly septic with extensive ulcerative lesions in the throat, extreme cervical adenitis, high fever, nephritis, and delirium. A fourth case entered the hospital on the sixth day of illness in delirium with extensive ulcerative tonsillitis and pharyngitis and hemorrhages from the mucous membrane. The fifth case entered the hospital on the fourth day in coma and died in four hours. All the fatal cases appeared hopeless from the time they entered the hospital. The effects of the injection of the serum and blood of convalescents as reported by the various observers correspond to those noted by us. There is quite constantly a fall of temperature beginning two to four hours after the injection and reaching its limit in

12 to 24 hours. In purely toxic cases the temperature falls to nearly normal and shows little tendency to subsequent rise. In cases with septic complications also the fever falls at first but usually rises again somewhat later. More striking than the fall of fever is improvement in the general condition of the patient. Delirium subsides, the pulse becomes slower and its quality improves, cyanosis disappears, and in 12 to 24 hours a patient appears on the road to certain recovery while before the condition appeared almost hopeless. The most marked results occur in early cases. These terminate almost by crisis, the fever becoming quickly normal, the rash fading rapidly, and the patient entering at once on convalescence.

The donor of the blood must be free from tuberculosis and syphilis. If serum is used, blood is drawn from the vein at the bend of the elbow in a sterile manner, at the end of the third or fourth week of the disease, and the serum is allowed to separate after clotting. The serum is then drawn off and tested for sterility. Several serums are mixed and 30 to 100 c.c. of the mixture are injected intramuscularly, usually into the mass of muscles over the outer sides of the thighs. The serum may have 0.2 per cent. of trikresol added. Fresh serums seem more effective. When serums have been kept for several months they appear to lose much of their activity. The advantages of serum over the whole blood are that serum may be kept for some time until needed and that several serums may be mixed. Previous collection is essential in order to have serum available when needed in smaller hospitals. In large hospitals where suitable patients are constantly available for bleeding, freshly drawn blood may be used as advised by Zingher.[127] Wassermann tests are previously made on all suitable cases so that they may be bled whenever a case requring the treatment presents itself. Two ounces of blood are added to 2 c.c. of sterile 10 per cent. sodium citrate solution, and this is injected intramuscularly in doses of 2.5 to 8 ounces, the injection being divided among several points. Absorption quickly occurs. In septic cases Zingher[128] recommends intramuscular injections of citrated fresh normal blood in doses of six to eight ounces which may usually be secured from members of the patient's family.

Since this chapter was written and the final proofs read such important additions to our knowledge of scarlet fever have been announced that it seems desirable to include a consideration of them.

The relationship of streptococci to scarlet fever has long been a subject of dispute. Reference has already been made to observations bearing upon the association of hemolyzing streptococci with scarlet fever and to studies which had suggested that such streptococci have specific biologic properties which differentiate them from streptococci from other sources. Of numerous attempts to produce scarlet fever in experimental animals with scarlet fever secretions and cultures of streptococci none has yielded convincing results. An instance of human scarlet fever which apparently was due to accidental inoculation with a streptococcus culture in a laboratory worker was reported by

Krumwiede, Nicoll and Pratt.* It remained for George F. Dick and Gladys H. Dick to produce scarlet fever in man by purposeful inoculation with streptococci from cases of scarlet fever. The cultures were rubbed over the tonsils of susceptible persons, and scarlet fever followed.† Charlton‡ had found that the blood serum from persons convalescing from scarlet fever and from some normal persons, if injected into the skin of persons with a scarlet fever rash, caused local blanching. These results were also obtained by others, but the fact that many normal serums acted equally well as did convalescent scarlet fever serum in causing blanching, threw doubt upon the specificity of the reaction. Mair§ found that blanching of the scarlet fever eruption follows the injection of serum from persons convalescent from scarlet fever and from many normal persons. The serum from some persons, especially those of an age when the susceptibility to scarlet fever is greatest, did not cause blanching, Mair believed that the eruption of scarlet fever was due to a toxin formed during the disease and that recovery followed the production of an antitoxin. The blanching phenomenon he ascribed to the local action of antitoxin contained in the serum of convalescent scarlet fever patients, and in the serum of persons who had previously passed through attacks of the disease, many mild and unrecognized.

While evidence was accumulating that the cause of scarlet fever acted through a toxin which it produced, and the recovery followed the elaboration of a neutralizing substance or antitoxin, the final proof of this seems to have been secured by the convincing experiments of the Dicks.‖ Dilute sterile filtrates of cultures of scarlet fever streptococci were shown to cause a local reaction when injected into the skin of persons at the beginning of scarlet fever and of some normal persons, while no reaction followed such injections in persons convalescent from scarlet fever and in many normal persons. Reasoning from analogy the persons who gave no reactions were considered immune to scarlet fever, probably from previous attacks. This cutaneous test has become known as the Dick test, and corresponds to the Schick test for diphtheria immunity. If the toxic filtrate is mixed with serum from persons convalescent from scarlet fever no reaction follows its injection in persons who show a reaction with the original filtrate.

Assuming that persons who develop a positive reaction with the intracutaneous toxin injection are susceptible to scarlet fever, the Dicks¶ have injected such with suitable amounts of the toxin with the purpose of producing immunity. A few hours after the injections there appear fever, general malaise, nausea, vomiting and sometimes a scarlet fever like rash. With smaller doses most or all of these symptoms are absent. Following these injections the skin test becomes negative, and the blood serum of such immunized persons has the property of neutralizing the toxin.

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*Archives of Internal Medicine, xiii (1914), p. 909.

†Jour. Amer. Med. Assoc., lxxxi (Oct. 6, 1923), p. 1166.
Jour. Amer. Med. Assoc., lxxxii (Jan. 26, 1924), p. 301.

‡Ztschr. f. Kinderheil, xvii (1918), p. 328.

§Lancet, ii (Dec. 29, 1923), p. 1390.

‖Jour. Amer. Med. Assoc., lxxxii (Jan. 26, 1924), p. 265.

¶Jour. Amer. Med. Assoc., lxxxii (Feb. 16, 1924), p. 544.

These investigators have also produced a scarlet fever antitoxin by injecting sterile streptococcus filtrates into horses.* The antitoxin can be separated from the whole serum by the method of chemical precipitation used in preparing diphtheria antitoxin.

The scarlet fever serums previously produced from horses by injecting killed or living cultures of streptococci have not proved entirely satisfactory. Such serums at times, as those of Moser and more recently of Dochez and Sherman,† appear to favorably influence the course of scarlet fever, but the antibody content has been so small that large amounts of serum must be administered with resulting severe serum reactions. The presence of antitoxin in the serum prepared by Dochez and Sherman is evidenced by its ability to blanch the scarlet fever eruption when injected into the skin. It is to be hoped that the separation of the toxin in solution will allow immunization of the horse to a higher degree, and that by a process of precipitation a much less toxic product may be secured.

The use of toxin for active immunization by the Dicks recalls some extensive vaccination procedures which were carried out some years ago in Russia. In 1905, Gabritschewsky,‡ Director of the Bacteriologic Institute in the Royal University at Moscow, began to employ injections of a streptococcus vaccine as a preventive against scarlet fever. He was soon followed by many other physicians in Russia. They employed bouillon cultures of scarlet fever streptococci, devitalized by heating at 60°C. and with 0.5 per cent. phenol added. The primary dose was 0.5 c.c. for children of 2 to 10 years of age to 1.0 c.c. for older persons. For children below 2 years smaller doses were used. Three injections were given at 7 to 10 days intervals, each succeeding dose being 1½ to 2 times the former one. An excellent review of the literature on the use of this measure in Russia was prepared by Smith.§ The reactions observed following the primary injections correspond to those described by the Dicks after injections of the toxic filtrate, namely fever, local redness and tenderness, headache and malaise. Sometimes there was vomiting and a scarlatinal eruption, not followed by desquamation. In persons who had scarlet fever previously, no reaction occurred. Over 50,000 vaccinations were made, and apparently satisfactory protection was secured as shown by the statistics. Owing to the circumstances of use, mostly in country villages, and to the publications being almost entirely in Russian, little attention was given the results in western Europe and America. It now seems that these observers were injecting the soluble toxin in the killed cultures, although perhaps not in a concentrated form, and that for twenty years too little attention has been given this remarkable human experiment. In his publication in 1906, Gabritschewsky significantly remarks—"The involvement of the isthmus faucium after vaccination as also the exanthem are most naturally explained as due to the action of toxin."

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* Jour. Amer. Med. Assoc., lxxxii (April 19, 1924), p. 1246.

† Jour. Amer. Med. Assoc., lxxxii (Feb. 16, 1924), p. 542.

‡ Cent. f. Bakt., Orig., xli (1906), p. 852.

§ Boston Med. and Surg. Jour., clxii (Feb. 24, 1910), p. 242.

The establishment of streptococci as the cause of scarlet fever, the Dick cutaneous test by which individual immunity and susceptibility may be determined, the immunization of susceptible persons by injections of the soluble toxin, and the production of antitoxin in horses by the injection of the toxin establish conditions as regards prevention and cure of scarlet fever which are parallel to those obtaining in diphtheria. The standardizing of the toxin and antitoxin of scarlet fever presents more difficulty than is met with in those of diphtheria. In the latter the uniformly susceptible guinea pig furnishes a reliable test animal, while in scarlet fever the tests must be made upon susceptible human individuals, no suitable animal, so far as known, being available.

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CHAPTER CLV

MEASLES

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Definition.—Measles is an acute specific infectious disease, highly communicable, which manifests itself by catarrhal symptoms and a characteristic eruption.

Etiology.—A number of investigators have produced measles experimentally in monkeys by injecting the blood of patients with measles taken from 24 hours before to 36 hours after the appearance of the eruption. Hektoen[1] has produced the disease in human beings with similar injections of blood. The researches of Anderson and Goldberger[2] have led to the following conclusions: (1) The virus of measles as it exists in the circulating blood, in a certain proportion of cases is capable of passing through a Berkefeld filter. It is therefore a filterable virus. (2) It resists drying and freezing for 24 hours. (3) It is destroyed by exposure to a temperature of 55°C. for 15 minutes. (4) It retains some infectivity after 24 hours exposure at 15°C. (5) The blood is only infectious for 24 hours before to 24 hours after the appearance of the eruption. (6) The infectivity disappears with the approach of convalescence. (7) The desquamating scales are not infectious. (8) The incubation period in the monkey is from 5 to 22 days, usually from 8 to 10 days. (9) Inoculated monkeys may give a febrile reaction without the appearance of an eruption. Such monkeys however are immune to a subsequent inoculation. (10) Blood cultures are negative. Recently Tunnicliff[3] has described a diplococcus which she found almost constantly in the blood during the pre-eruptive and eruptive stages, and also in the secretions of the throat, nose, and eyes. With the assistance of Dr. Lenz, I have made blood cultures from a number of patients during the pre-eruptive and at the beginning of the eruptive period, using various media, including those recommended by Tunnicliff, but all our cultures remained sterile.

Susceptibility and Immunity.—A small number, approximately 3 per cent. of all individuals are naturally immune. This is a real immunity and is not due to lack of exposure or to an unrecognized mild attack Occasionally, a child escapes infection at the first exposure, and is infected later. I have seen several of such cases. In large centers where measles is endemic, infants under two months of age are practically immune. They usually escape infection even when freely exposed. Some years ago the following case came under my observation. A wet nurse who had contracted measles from one of the older children of the family, continued to nurse regularly an infant of five weeks of age, without infecting the latter. As the infant grows older this immunity gradually disappears, so that at eight months of age it is usually entirely lost. This difference in susceptibility between those under and those over eight months, can be demonstrated in various ways. The table indicates the number of days which elapsed from the time of infection to the appearance of the eruption in 300 patients. Of these 63 were under eight months, and 237 were over eight months of age.

Day eruption	10	11	12	13	14	15	16	17	18	19	20	21
	Per cent.											
Over 8 months...	1.5	6.3	20	31	23	11	4	2.2	0.7	0.7		
Under 8 months..	...	4.7	9.5	22	6.3	24	14	9.5	4.7	1.6	1.6	1.6

It will be seen that the eruption appeared on or before the fourteenth day in 81.4 per cent. of the older group, and in only 42.5 per cent. of the younger group. This prolonged incubation would tend to indicate a relative immunity in young infants. In families in which there were several children, I have frequently noted this difference in the period of incubation between the infants under eight months and the older children. The following is an example. In a family in which there were three children, the oldest contracted measles, and was isolated before the eruption appeared. However the other two children had been already infected. The older who was two years of age had the initial fever on the tenth day, the eruption on the thirteenth day; the younger eight months of age, had the initial fever on the fifteenth day and the eruption appeared on the eighteenth day. This relative immunity of young infants is also indicated in the mild course of the disease, and the slight amount of constitutional disturbance. Of 59 patients under two years of age, 17 were under eight months, 42 between eight months and two years. Of the younger group only 41 per cent. showed a loss of weight during the period of incubation, whereas of the older group 76 per cent. showed such a loss. This relative immunity of infants under eight months of age, is probably conveyed by the mother, who has had measles, through the placental circulation, not through the breast milk, for I have found that artificially fed as well as breast fed infants enjoy it. It is not surprising that it should gradually disappear. In this connection the experimental work on mice by Ehrlich is interesting. He found that if female mice were immunized against the castor oil poison (rizin) during pregnancy, the young enjoyed an immunity against this poison, but only for 40 days. It is only in localities in which measles is endemic that young infants possess this immunity. In such large centers, practically all children are infected sooner or later, so that almost all mothers have had the disease, and can convey this temporary immunity to their offspring. On the other hand, in isolated places, where epidemics of measles occur only at long intervals, it is possible for women who have never had measles, to give birth to children, who would not be immune during the first few months. In epidemics which occurred in some of the isolated islands of the Atlantic ocean, infants under five months were infected as frequently as older children. Infants born of mothers who have had measles during pregnancy are not permanently immune. The difference in the prevalence of the disease in small isolated places as against the larger centers of population, may possibly account for the difference of opinion among authors as to the frequency of measles in infants under five months of age.

One attack of the disease renders the individual immune to subsequent infection. In the experimental work of Anderson and Goldberger, it was shown that monkeys that had been successfully inoculated, even if they only had a febrile reaction, were immune to a second inoculation. This agrees with our clinical experience. Every physician can cite a large number of cases from his own practice. As an instance of repeated exposure without infection, after the first attack, I can cite the following. In a family in which there were seven children, aged 16, 11, 10, 8, 7, 5 and 2 years, the two oldest children had measles in 1906. They were in intimate contact with the other five children, who each had an attack of measles in turn in 1907, 1909, 1910, 1912 and 1916, but they did not contract the disease a second time. A few undoubted instances of a second attack have been reported, but considering the widespread prevalence of the disease they are extremely rare. In many cases we hear of second and third attacks, but in such cases an incorrect diagnosis has probably been made. The presence of fever, catarrhal symptoms, and a morbilliform eruption are not sufficient in order to make a positive diagnosis. The pathognomonic manifestations in the mouth must also be present.

Age and Seasonal Incidence.—A small number, about twenty, well authenticated cases of measles in the newborn have been reported. The infection may take place in utero, from a mother who has contracted the disease at the end of pregnancy. In such a case the infant may be born with the eruption, or the eruption may appear a few days after birth; or it may be infected by the mother in the usual way, shortly after birth. I have seen measles in an infant 16 days old. The mother had the prodromal catarrh shortly after labor, and the eruption appeared three days later. Although young children are most susceptible to infection, persons of all ages, who have not had an attack may contract the disease. The age incidence is shown in the following chart (Fig. 42). It will be seen that the disease is most common between one and six years of age, and then rapidly declines.

Seasonal Incidence.—This can be studied best in large centers of population, where the disease is endemic, and therefore an opportunity for the spread of the disease is always present. In New York City (Fig. 43) the highest point is reached in March and April, the lowest point occurs in September. The opening of the schools and kindergartens in the latter month is probably partly responsible for the gradual rise in the number of cases noted in October, but this rise is *gradual*, and the marked increase does not occur until March. Almost all of the communicable diseases are at their lowest point in September. In the case of measles, this cannot be due to the fact that the windows are kept open, or that there is absence of close confinement, for these factors are also present in the four preceding months in which the number of reported cases is much greater. In New York City there are always a certain number of cases of measles, the disease is very markedly communicable by contact, so that exposure must frequently occur even during the late summer and early fall months. A low virulence of the infectious agent has been assumed by some authors, but I have not observed that the cases which occurred in the fall were milder in character. According to my own observations, the virulence of the infectious material appears to have remained the same during the last few years. The difference in the course of the disease in different children, is due I believe to a difference in the individual reaction to the infection. It is possible that at certain seasons of the year, the vast majority of children elaborate a protective mechanism, which renders them more resistant to certain kinds of infection, but that a small percentage lack this, and become infected. It would be interesting to note, whether children who escaped infection on exposure in the fall, were subsequently infected on exposure in the spring.

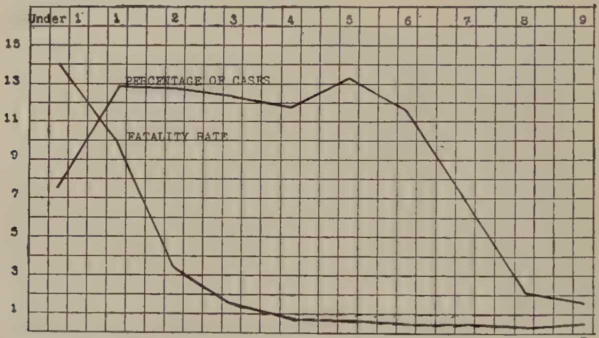

Fig. 42.—Showing the distribution of measles by age and the fatality rate for each age period; Aberdeen, Scotland, 1883–1902. (Crum.)

Age	Percentage	Fatality Rate Per 100 Cases
Under 1 year	7.5	14.0
1 year	12.9	10.0
2 years	12.8	3.4
3 years	12.5	1.6
4 years	11.8	0.9
5 years	13.3	0.7
6 years	11.5	0.5
7 years	7.0	0.5
8 years	3.1	0.4
9 years	1.6	0.6
Over 10 years	5.5	0.5

Mode of Infection.—It has been demonstrated that the infectious material is present in the discharges from the nose and mouth and it is a significant fact, that the diseases which are the most readily communicated, namely, measles, whooping-cough and influenza, are associated with sneezing and coughing. In the vast majority of cases, measles is spread by *direct contact*. The evidence in favor of infection through inanimate objects is far from conclusive. For example: As an illustration of the possibility of the infectious material being carried by a letter, the case reported by Davies is frequently cited. Briefly, the case was as follows. A young man was found on examination to have measles, "the rash was fully out." "Visiting him the following day the diagnosis was amply verified, but the symptoms were so slight that he sat up in bed, and wrote a letter to a brother. His brother

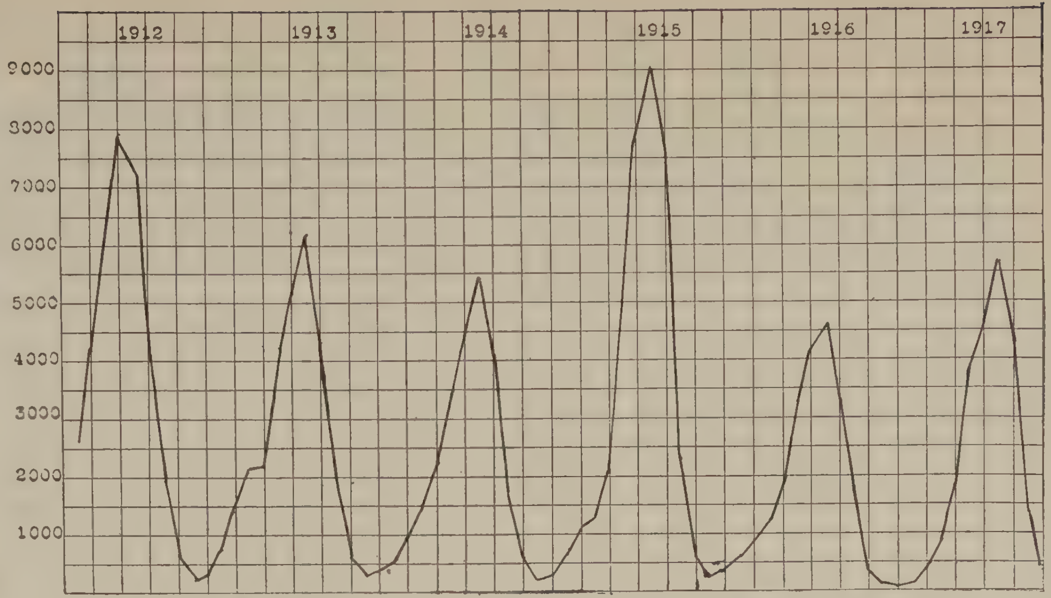

FIG. 43.—The seasonal incidence of measles, New York City, 1912–1917.

	1912	1913	1914	1915	1916	1917
Jan.	2670	2126	1519	1355	1242	899
Feb.	4219	2169	2190	2067	1894	1781
Mar.	7713	4369	3483	5053	3281	3914
Apr.	7938	5256	4485	7849	4208	4634
May	7272	6231	5483	9088	4579	5736
June	4132	4471	4094	7602	3393	4355
July	1982	1982	1734	2486	1813	1368
Aug.	604	576	534	615	417	480
Sept.	221	283	244	270	119	
Oct.	317	384	324	325	74	
Nov.	769	548	679	581	127	
Dec.	1420	946	1024	895	456	

was attacked by measles." The number of days which elapsed from the receipt of the letter to the appearance of the eruption is not mentioned by Davies, although this is an exceedingly important point. It is stated that the rash was "fully out" on the day preceding the writing of the letter. It is pretty generally agreed, that after the eruption is fully out, the disease is no longer communicable. In such an unusual occurrence we are certainly justified in requiring more definite evidence. The *room* occupied by a patient does not retain the infectious material in a virulent form. As a medical inspector in the Department of Health of the City of New York, on several occasions I had an opportunity to observe that when a family with susceptible children moved into an apartment which had just been vacated by a family with children who had just recovered from measles, they did not contract it. It has also been noted that children who occupy a classroom in school in which a case of measles occurred are not infected. Flindt records an instance in which the same room was used by one class in the forenoon, another in the afternoon. When the disease broke out in the first group, the other did not become infected. The evidence in favor of infection through a third person, is hardly more convincing. Without denying absolutely the possibility of such infection, it may be safely said that such transmission is exceedingly rare.

Duration of the Infective Period.—The time of greatest infectivity is at the height of the catarrhal symptoms, one or two days before the eruption appears. It is still infectious during the stage of efflorescence, and then rapidly disappears with the drop of the temperature in uncomplicated cases. The entire period of infectivity is probably no more than four or five days. Clinically we know that fourteen days usually elapse from the time of infection to the appearance of the eruption. The first distinct manifestation of the disease, fever, usually appears in secondary cases ten days after the prodromal catarrh of the primary case, and the eruption follows three or four days later. This interval is fixed and definite. If the disease were communicable for more than five days, we should expect a certain percentage of secondary cases to occur after a longer interval, namely, from fifteen to twenty days. If a child escapes infection in the catarrhal stage of the primary case, it is not infected in the convalescent stage, but is infected in the catarrhal stage of the secondary case. On several occasions I have admitted a child with a fading measles eruption to the ward, usually for pneumonia or colitis, and have not seen other susceptible children in the same ward infected.

Incubation.—Strictly speaking the period of incubation should be limited to the interval which elapses from the time of infection to the appearance of the first definite symptom, which is the initial fever. This can be determined very accurately. The same cannot be said of the appearance of Koplik's spots, the catarrh, or even the eruption. In Hektoen's experimental inoculations in human beings, the initial rise of temperature occurred at the end of seven or eight days. In Anderson and Goldberger's experimental inoculations in monkeys, the initial rise of temperature occurred in most cases after 10 days. I have been able to determine pretty accurately the period of incubation in 300 patients. The following table shows that the earliest symptom was the initial fever which was usually present on the tenth or eleventh day (56 per cent. of the cases), the catarrhal symptoms were most frequent on the eleventh or twelfth day (60 per cent.), the tonsillar spots when present, appeared with about equal frequency on the ninth, tenth, eleventh, twelfth and thirteenth day, the Koplik spots were most frequently seen on the eleventh or twelfth day (54 per cent.), and the eruption appeared most frequently on the twelfth, thirteenth or fourteenth day (67 per cent.). Although the period of incubation in the strict sense, is usually 10 days, it may be as short as seven or as long as 14 days, the longer incubation period being much more common in infants under eight months of age.

Days from infection	7	8	9	10	11	12	13	14	15	16	17	18	19
	Per cent.												
Fever	4.0	6.3	13	33	23	7.6	6.3	4.3	1.0	0.6			
Catarrh	0.4	0.7	4.7	14	34	26	9.8	5.0	1.5	2.5	1.1	0.6	
Tonsillar spots	4.0	...	14	16	25	22	18						
Koplik spots	...	...	2.8	10	28	26	18	7.4	2.3	2.8	0.9	1.0	
Eruption	...	...	....	1.5	6.0	18	29	20	13	6.0	3.5	1.5	0.6

Pathological Anatomy.—With the exception of the changes in the skin, strictly speaking there is no pathological anatomy peculiar to measles. The changes in severe fatal cases which come to autopsy, are due to the complications or sequelæ. The intensity of the changes in the skin and mucous membranes, except in those patients who have hemorrhages, is markedly diminished after death. The swelling, which is usually most distinct in the face, is due to an exudation and edema. The inflammatory changes in the skin are less intense than those in scarlet fever. There is a dilatation and congestion of the smaller veins and capillaries of the papillæ; a leukocytic infiltration along the walls of the smaller blood-vessels, and a distention of the lymph spaces. These changes are more marked in the upper layer of the skin, as these parts are richest in blood-vessels. The hair follicles and the sebaceous glands which are surrounded by a capillary network, are infiltrated with round cells. It is this infiltration which causes the papular elevation so characteristic of the measles eruption. The catarrhal changes in the mucous membrane are usually more marked than in other infectious catarrhs, the submucosa is more intensely involved, and the extravascular infiltration is greater. Catarrhal changes of varying intensity are present in the eyes, ears, nose, and throat, and in the larynx and bronchi. When the catarrhal changes descend into the bronchioles and into the air vesicles, there is an early cellular infiltration of the peribronchial and perivascular connective tissue, and the changes characteristic of bronchopneumonia result. Occasionally a membranous pharyngitis or laryngitis is found. In severe cases there is a marked cellular hyperplasia of the lymphatic structures, the superficial lymph-nodes, and the lymphatic tissue of the naso-pharynx, tongue, and the intestinal tract are swollen. The hyperplasia of the spleen is not marked. The heart, more especially the endocardium may present inflammatory changes, less frequently the pericardium and myocardium. The kidneys are much less frequently affected than in scarlet fever, and when involved show changes similar to those found in that disease, namely a glomerular nephritis.

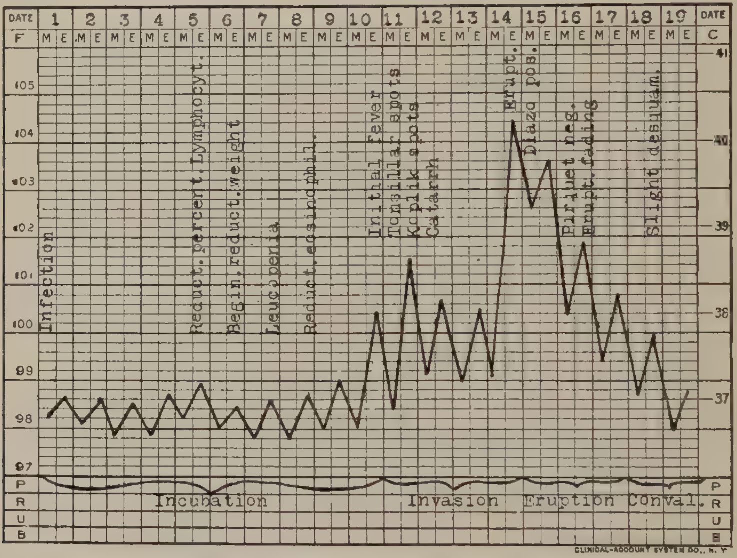

FIG. 44.—Diagrammatic representation of the course of an attack of measles. Showing the four stages of the disease.

The bacterial examination of the secretions of the respiratory tract usually shows the presence of streptococci, staphylococci, or pneumococci.

Symptomatology.—The course of the disease is divided into four periods (Fig. 44) the period of incubation, from the time of infection to the appearance of the first definite symptom, which is the initial rise of temperature. This usually lasts 10 days. The period of invasion, in which the prodromal catarrh and the oral manifestations are the chief symptoms. This usually lasts from three to four days. The period of eruption, which usually lasts three days; and the period of convalescence, which lasts from three to four days in uncomplicated cases.

The period of incubation is usually free from any distinct symptoms; a slight rise of temperature, soreness of the throat, headache or drowsiness may be present, but it is difficult to determine whether this is a part of the disease, or due to some mild intercurrent infection.

Loss in Weight.—In the vast majority of cases, the patients show a loss of weight during the latter half of the period of incubation. In 96 children over eight months of age, I found the average loss 5.7 oz. On the other hand in 33 infants under eight months the average gain was 2 oz. This indicates as I have already mentioned that in the young infants the disease runs a milder course, and the appetite and sleep are not so often disturbed.

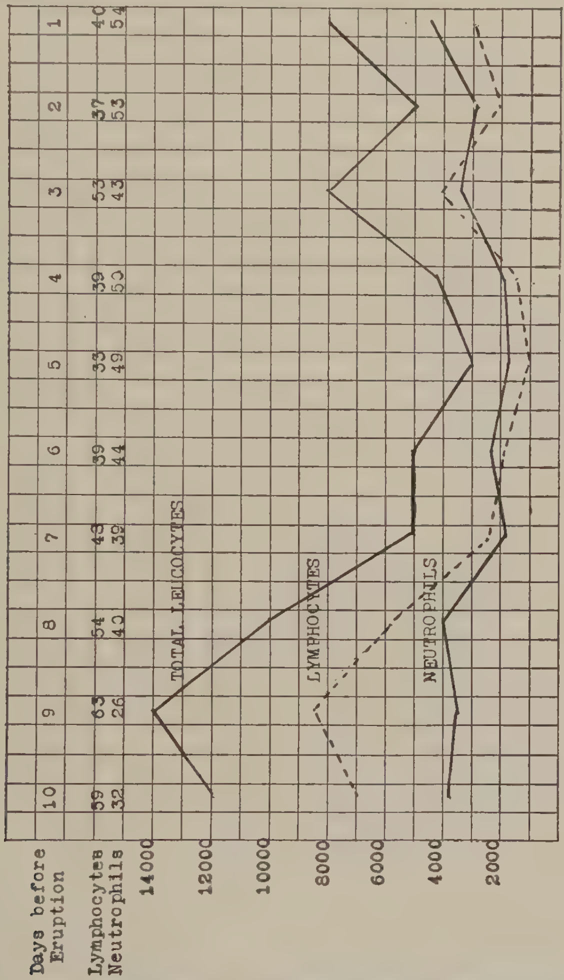

FIG. 45.—The changes in the blood picture, in the period of incubation and invasion, in measles. (Hecker.)

Blood Changes.—The daily examination of the blood may be of diagnostic value. Unfortunately, it can only be carried out in hospital practice. Hecker's[4] investigations have shown that there is usually a reduction in the relative percentage of the lymphocytes, beginning six days before the eruption appears (Fig. 45). About four days before the appearance of the eruption there is a marked leukopenia, so that there is an absolute as well as a relative reduction in the lymphocytes, and beginning three days before the appearance of the eruption, there is a progressive diminution in the number of eosinophile cells. I have sometimes found the blood examinations of value in the early detection and isolation of secondary cases in the hospital ward. However the initial rise of temperature in afebrile patients, is a much simpler and much more reliable guide. A distinct leukocytosis after the eruption is complete may indicate some complication.

The Period of Invasion.—A rise of temperature is always the first symptom. It may be slight, but if the temperature is taken several times a day, it will always be detected. There is nothing characteristic of temperature curve, but certain types are more common in simple uncomplicated cases. All the curves show more or less remission in the morning hours. In all the temperature charts, in order to show the type more clearly, only the maximum and the minimum temperature each day is indicated. A common type is that which presents a gradual rise and a critical fall (Fig. 46). This is present in about 50 per cent. of all cases. Another slightly less common form is that in which there is a gradual rise and a lytical fall (Fig. 47). A marked remission or even intermission of 24 to 48 hours is not uncommon (Fig. 48). This is always suggestive, as it rarely occurs in other diseases. In some of these cases, on account of the catarrhal symptoms and the exposure to infection, measles is suspected, but the drop

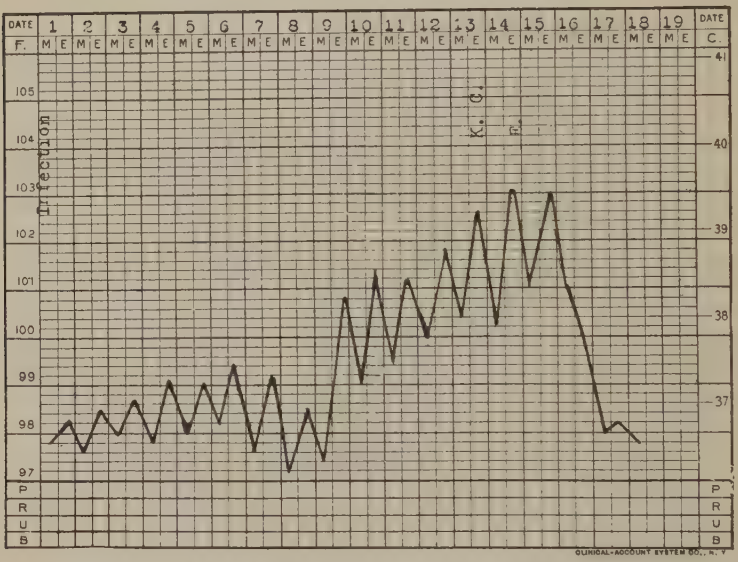

FIG. 46.—Temperature curve in uncomplicated measles. Showing a gradual rise and a critical fall. K = koplik spots. C = catarrh. E = eruption.

in the temperature may lead the inexperienced astray. If the patient is seen for the first time in this afebrile interval, one of the other early

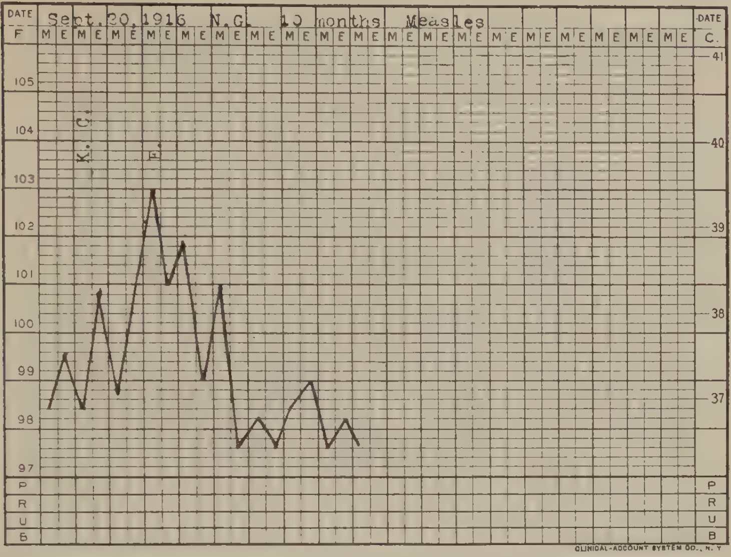

Fig. 47.—Temperature curve in uncomplicated measles. Showing gradual rise and lytical fall. Patient, a boy 10 months old.

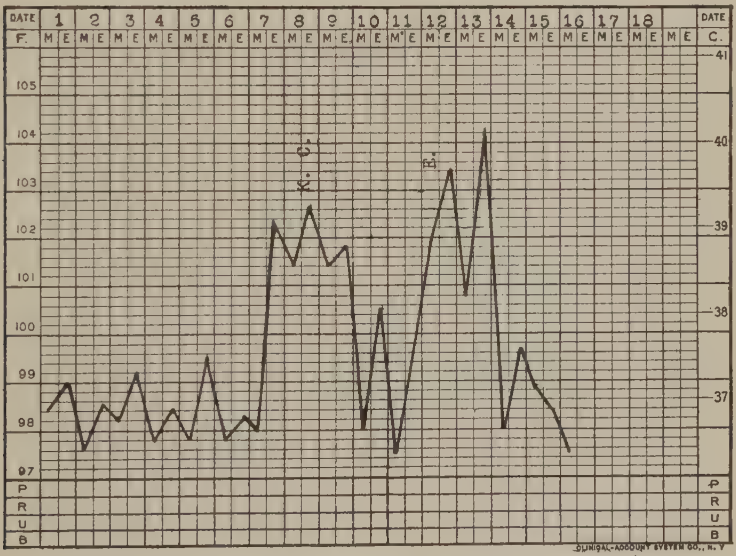

Fig. 48.—Temperature curve in uncomplicated measles. Showing a remission between the initial rise of temperature and the eruption.

manifestations, such as the tonsillar or Koplik spots may seem to be the first symptom. There may be a short period of incubation, an early initial rise of temperature, and a prolonged invasion (Fig. 49). In many of these patients, the high temperature, increased respiration, and bronchial râles, often lead to an incorrect diagnosis of pneumonia, but the appearance of the eruption, followed by defervescence makes the diagnosis clear.

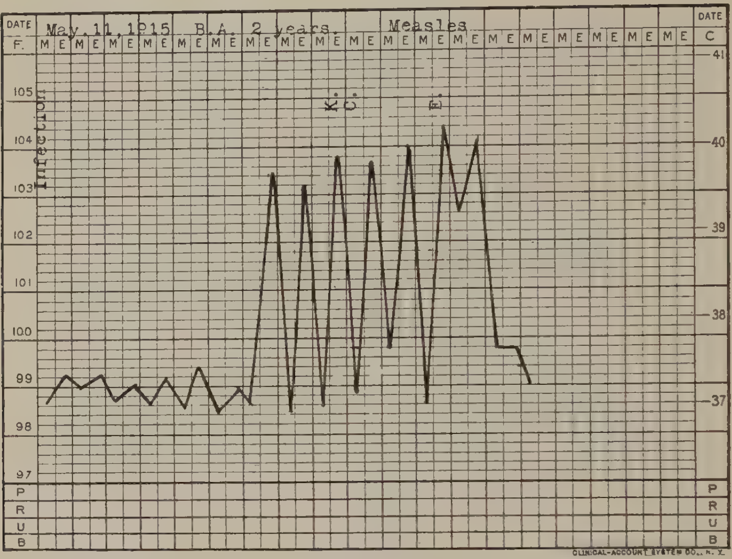

FIG. 49.—Temperature curve in uncomplicated measles. Showing a short incubation, a long invasion, and a critical fall in temperature.

Time of the Maximum Temperature.—In a series of 169 uncomplicated cases the maximum was under 101 degrees in five; between 101 and 102 degrees in seven; between 102 and 103 degrees in 25; between 103 and 104 degrees in 71; between 104 and 105 degrees in 43; between 105 and 106 degrees in 16; and over 106 degrees in two cases. Almost all of the patients in whom the maximum temperature was under 102 degrees were under eight months of age. The majority of the patients had a maximum temperature between 103 and 105 degrees, the larger number of these having between 103 and 104 degrees. The maximum temperature occurred in 51 cases before the eruption appeared; in 72 cases during the first 12 hours of the eruptive period, and in 46 cases from 12 to 24 hours after the eruption appeared. It is frequently stated that the maximum temperature usually occurs at the height of the eruption. This is incorrect, and is probably based on the records of hospital cases, which are usually admitted several hours after the eruption has appeared. The time at which the maximum temperature is reached is dependent, to a certain extent on the time at which the eruption begins to appear. If this occurs in the morning, the highest point is reached on the afternoon or evening of the same day. If the eruption appears in the evening, the highest point is usually reached at that time, and the remission of the following morning is slight.

Catarrhal Symptoms.—The changes in the mucous membranes manifest themselves by the presence of sneezing, swelling of the nasal membrane, associated with more or less nasal obstruction, a mucus discharge, and sometimes epistaxis. There is a redness and swelling of the conjunctiva, and frequently small bluish-white specks can be seen on the injected caruncle. Somewhat later there is a sensitiveness to light, and a mucopurulent discharge from the eyes, with a tendency for the lids to become matted together especially in the morning after the night's sleep. The cough is usually dry and the voice somewhat hoarse as a result of the catarrhal condition of the larynx.

Mouth.—The same infectious agent causes the changes in the skin and in the mucous membranes. The difference in the time of their occurrence, and in the appearance which they present is due to the difference in the blood supply, and in the character of the tissues involved. The greater the blood supply the earlier and more distinct the manifestations. For this reason the changes are observed earlier in those parts which are very vascular or hyperemic. The difference in the appearances of the oral changes are due to the difference in the blood supply and structure of the cheeks, soft and hard palate, tonsils, tongue, and the gums.

Koplik's Spots (Koplik[5]).—These consist of bluish-white specks found most frequently and most distinctly on the buccal mucous membrane opposite the molar teeth, and on the inside of the lips. These specks are usually, but not invariably, surrounded by a narrow zone of red color. The predilection for the buccal mucous membrane and inside of the lips, may be due to the pressure of the teeth, which causes slight hyperemia at these points, for the spots are sometimes absent in young infants who have no teeth. These spots are present in 90 per cent. of all cases, and are not seen in other condition. They differ considerably in their appearance at different stages of their development, and in different individuals. There may be only two or three, or the mucous membrane may be studded with them. Sometimes the appearance is that of a fine brany desquamation of the epithelium, or delicate sprue-like shreds may be seen. A good light, preferably daylight is essential in the examination. Not infrequently small hemorrhagic spots or points may also be seen on the mucous membrane of the cheeks or palate.

Throat and Palate.—On the first day of the fever the throat may be slightly reddened. On the following day the tonsils and the posterior part of the soft palate present a fairly well-marked redness, and the tonsils may be slightly enlarged. The small mass of lymphoid tissue just above and to each side of the uvula may be swollen. A little later an eruption may be seen on the anterior part of the soft palate and on the posterior part of the hard palate, which consists of round or more or less irregular bright-red spots which are not sharply defined, and which are slightly raised above the level of the mucous membrane.

These spots vary in size from the head of a pin to a grape seed; they are discrete or joined together in irregular groups. On the post part of the soft palate small vesicular projections may be seen.

Tonsillar Spots (Herrman[6]) (Fig. 50).—If the throat is carefully examined at the time of the initial rise of temperature, in about 40 per cent. of the patients, delicate spots will be noted on the tonsils. A good light is necessary, the tongue must be depressed, and a view of the entire tonsil obtained. These spots or streaks vary in size, number, shape and color. There may be only two or three, or there may be a very large number. They vary in size from the point, to the head of a pin; they may be seen as specks, round spots or streaks of irregular outline. The color seems to depend on the thickness of the exudate, and varies from a grayish-blue to white. These spots are seen only in the very *early* stage of the disease, and may be visible for 24 to 48 hours. They are more frequently and more distinctly seen on enlarged succulent tonsils. In a series of 35 patients in which these spots were observed, they were present one day before the eruption in nine, two days before in 11, three days before in seven, four days before in five, six days before in two, and nine days before the eruption in one patient. In 24 of the 35 patients the tonsillar spots were seen before the Koplik spots, in six at the same time, and in only five were the Koplik spots noted prior to the tonsillar spots. In all the 35 patients there was or had been a slight rise of temperature at the time the spots were seen, but in two-thirds of these the temperature was not over 101 degrees. This serves as a valuable point in differentiating these spots from those of follicular tonsillitis. In the latter, the temperature is usually much higher, and the constitutional disturbance is more marked.

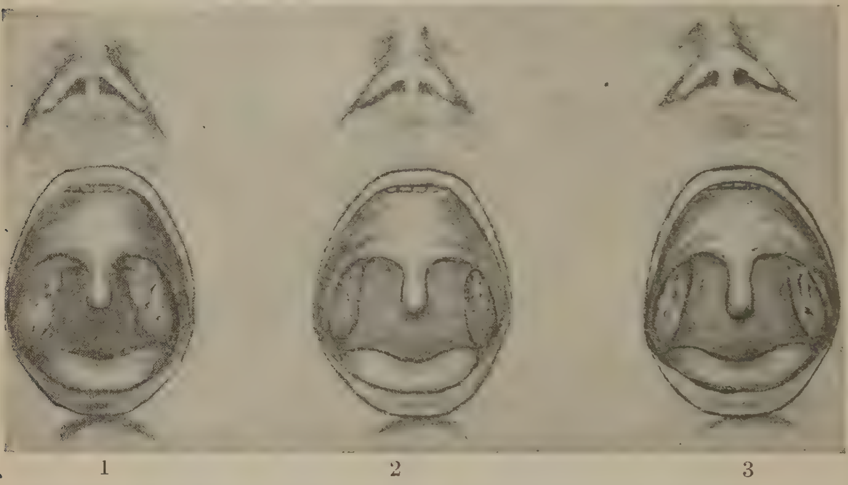

FIG. 50.—Tonsillar spots seen in the early stage of measles. 1, A few round spots about the size of the head of a pin. 2, A large number of very small spots or streaks. 3, A few irregular streaks.

Gums.—The so-called "Stomatite érythemato pultacée "of the French, Comby[7] usually precedes the appearance of the eruption, and is most distinct at the height of the catarrhal stage. The gums are red and slightly swollen, but do not bleed. They are covered with a thin bluish-white opalescent epithelial deposit, which gives the gums the appearance of having been touched with a solution of nitrate of silver. This deposit may cover small or large areas. It is not pathognomonic of measles, as it may be present in scarlet fever and in influenza, but it is absent in rubella and in morbilliform eruptions due to other causes.

Eruption. Pirquet's Hypothesis.[8]—A few years ago von Pirquet developed the following hypothesis, in an attempt to explain the occurrence of the eruption, and the order in which the various parts of the body become involved. The exciter, that is the measles virus, enters the body and causes the infection. The infectious material gradually increases, and after 10 days the antibodies appear in the circulating blood. The contact of exciters and antibodies causes the formation of a hypothetical apotoxin. This clash between exciters and antibodies is the cause of the initial fever. The antibodies impregnate successively different parts of the body, first those portions richly supplied with blood-vessels, namely, the mucous membranes. The contact of exciters and antibodies causes an agglutination in these parts, and sneezing, coughing, and the oral manifestations result. The skin of the face, head, and back, that is the parts nearest to the heart and the large blood-vessels become impregnated with antibodies

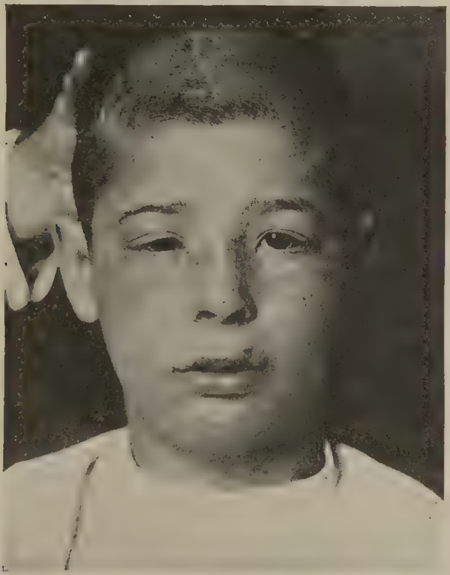

Fig. 51.—The eruption on the face in measles. Swelling of the face and eyes. (Photograph by Dr. William S. Gottheil.)

and meeting the exciters agglutination takes place and causes the appearance of the eruption in these parts. The skin of the trunk, extremities and buttocks in turn become impregnated and the eruption appears in these regions. The exciters are now nearly entirely agglutinated, the antibodies which reach the feet and elbows cause no agglutination, because the exciters have been used up, no apotoxin is formed, and these parts remain free from the eruption. The fever then disappears.

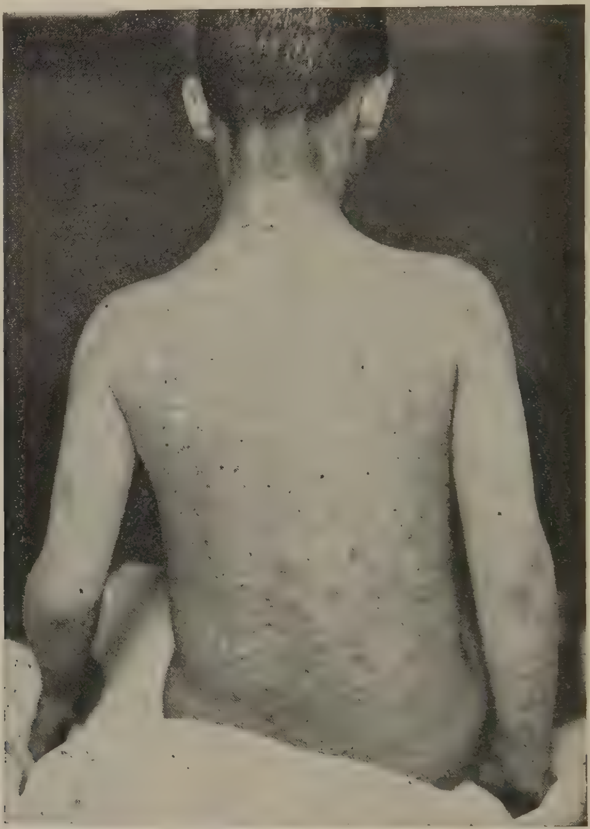

Fig. 52.—The eruption of measles. (Photograph by Dr. William S. Gottheil.)

Three or four days after the initial rise of temperature the eruption (Figs. 51, 52) begins to appear. The order in which the different parts are involved has been most painstakingly studied by von Pirquet (Fig. 53). In the following order of frequency, the spots may appear first behind the ears, in the middle of the upper part of the back, around the mouth and nose, on the cheek in front of the ears, or on the forehead. On the second day the eruption is distinct and profuse upon the face, head and the upper part of the back, and a small number of spots are seen on the chest, abdomen, shoulders and in the axilla.

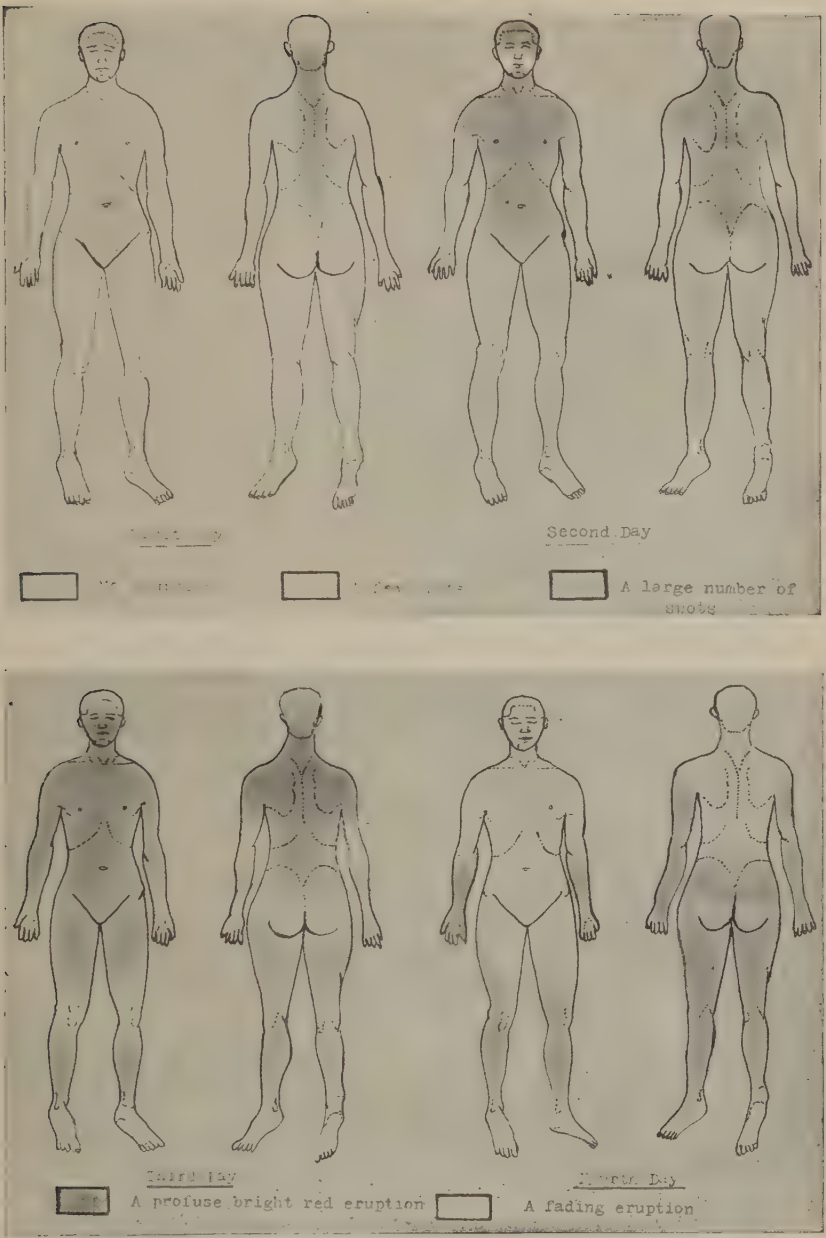

FIG. 53.—Distribution of the measles eruption. (After von Pirquet, in article on Measles in Nothnagel's Specielle Pathologie und Therapie, 1911.)

At this time a few papules may be seen on the arms, thighs, buttocks, and legs. On the third day, the trunk, shoulders, anterior surface of the arms, and thighs are covered with spots. The posterior surfaces of the arms, the forearms, the back of the thighs and legs show a small number of spots. A few scattered papules appear on the hands and knees. The feet and elbows may remain unaffected. The eruption is at first very red, but after one or two days the hyperemia diminishes. The eruption begins to fade on the second day on the forehead and face, on the third day on the trunk and shoulders, and on the fourth day on the extremities. On the fifth day slight pigmentation is seen on the affected parts. The cycle of development of the individual spots from the appearance of the macule to the disappearance of the hyperemia requires on the average three days. In the parts last affected, namely, the buttocks, hands and feet, the spots are less distinct and fade more rapidly, no pigmentation remaining. The individual lesion begins as a bright red follicular spot about the size of the head of a pin, round or irregular in outline. These spots increase in number, becoming somewhat darker in color, enlarge and tend to coalesce with adjacent spots. They are more irregular in outline and more prominent, so that they can be felt distinctly above the level of the skin. The variations from this normal course will be described later.

General Condition.—Just before and at the time of the appearance of the eruption, the patient becomes more apathetic, and takes very little interest in his surroundings. Sometimes headache and pains in the limbs are complained of. The pulse and respiration rate are proportional to the temperature. The catarrhal symptoms increase, the conjunctivitis and photophobia become more marked. The secretion from the nose may cause a slight excoriation of the upper lip, and the outlet of the nostril. The tongue is coated and may present a characteristic appearance. The coating is of a bluish-gray color, similar to that seen on the gums, except that it is not so uniform. Like the deposit on the gums it is probably due to the separation of the superficial epithelial layer. The appetite is poor. Vomiting and diarrhea may be present. The laryngitis becomes more severe and the cough more persistent. The examination of the chest shows a diffuse bronchitis. Numerous coarse mucus râles are heard all over the chest.

Lymph-nodes.—The cervical, axillary and inguinal nodes are often enlarged, even the epitrochlears may frequently be palpated. The spleen is seldom enlarged or palpable. One must be sure, especially in infants, that it was not palpable prior to the onset of measles.

Urine.—The urine is diminished in quantity, more concentrated, and of high specific gravity. When there is a very high temperature, small quantities of albumin may be found in the urine. The diazo reaction is positive, and a small amount of acetone and diacetic acid may be present. These changes are not characteristic of measles, but may be present in a number of acute infectious diseases.

With the completion of the eruption, a distinct change for the better takes place. The patient suddenly becomes brighter and more active, and is willing to take food. The temperature falls suddenly or gradually. Occasionally there is another slight rise of temperature, without the development of any complication. The pulse may be slow and even slightly irregular, but this irregularity disappears within a few days.

The foregoing represents the usual or normal course of the disease. However in a certain percentage of uncomplicated cases, the disease or one or more symptoms may run a somewhat different course.

Mild Form.—This is seen especially in young infants under eight months of age (Fig. 54). The incubation period is longer, the period of invasion shorter, the catarrhal symptoms may be slight, and Koplik's spots absent. The maximum temperature may not be over 101 degrees, and the constitutional disturbance so light, that the infant continues to take the breast regularly. In some the disease runs such a mild course that it may be overlooked if there is not another case in the same family. I do not believe that this difference is due to a lower virulence of the infectious material, but to a diminished susceptibility on the part of the young infant. A case recently seen will serve to illustrate. In a family in which there were three children, 5 years, 18 months, and 6 months of age, the oldest child contracted measles, which ran a normal course. The two other children were infected, the eruption appearing after 13 days in the child 18 months old, and after 16 days in the infant of 6 months. In the latter the disease ran an extremely mild course, the maximum temperature was

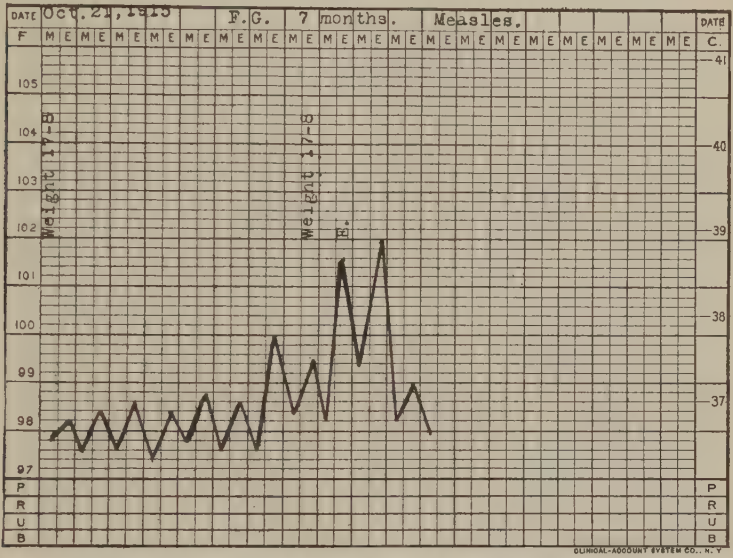

FIG. 54.—Temperature curve in a mild case of measles. Patient, 7 months old. No loss in weight and very slight constitutional disturbance.

101.5 degrees, the appetite was good, and the child continued to play. In the child of 18 months the disease ran a malignant course, complicated by stomatitis, otitis, and bronchopneumonia, and ended fatally. In a paper recently published Landé[9] describes seven cases of measles in infants, which occurred in a hospital service. All the patients were in poor condition. The first series of three children, aged 15 months, 9 months, and 13 months, had a severe form of the disease and died. The second series included four children, aged 7 months, 4 months, 11 months, and 8 months. Although they were in just as poor condition and exposed to the same possibility of cross infection, the disease ran a very mild course, with very little fever, or constitutional disturbance, and no loss in weight. The author is inclined to believe that the difference in the course of the disease in these two groups was due to a lowered virulence of the infectious material. I believe that it was due to the fact that three of the second group were under eight months of age. Heubner[10] reported two cases of measles in infants under five months of age. One was 15 weeks, the other 20 weeks old. In both, the disease ran a normal course. In the former, two other children of the same family had a very severe attack and died.

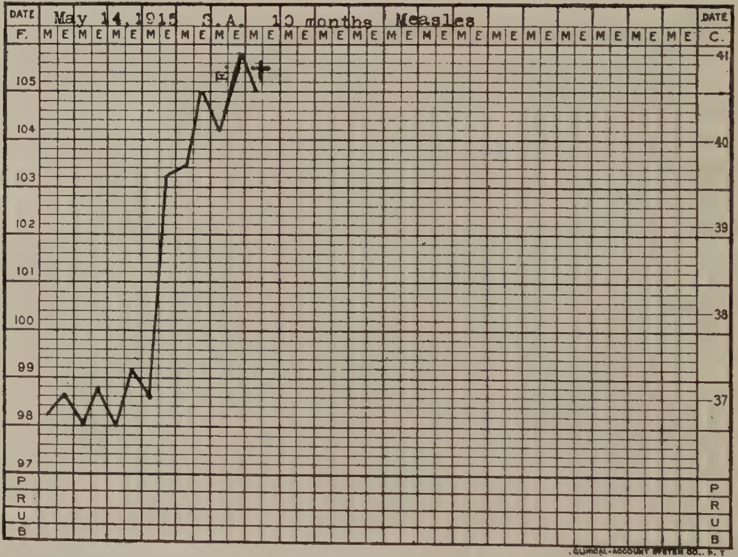

FIG. 55.—Temperature curve in a severe case of measles. High temperature. Death at time the eruption was beginning to appear. Patient, one of twins, ten months old.

Severe Cases.—In a small percentage of cases the disease runs a malignant almost fulminating course, not unlike that sometimes seen in scarlet fever and in meningococcus meningitis. The patient seems overwhelmed by the toxemia, offers very little resistance to the infection and often dies before the eruption appears (Fig. 55). In these cases the central nervous system seems to be profoundly affected, and the patient is prostrated. The eruption is very slow in appearing, and indistinct. The temperature increases, the stupor becomes more pronounced and life may terminate in convulsions.

Septic Cases.—In some severe cases it is difficult to determine, whether death is due to the toxemia of the primary disease or to secondary infection. In the excellent monograph by Landé[9] already referred to, 13 cases of measles with sepsis are reported. In eight a puncture of the heart was made just after death, and gave a positive result in six. The pneumococcus was found in three, the streptococcus in two, and the staphylococcus albus in one. The majority of these cases are associated with pulmonary complications. In a small number septic symptoms are present from the beginning, and there are no pulmonary complications. Metastatic ulcers and necrotic processes are often present, especially on the mucous membrane of the mouth.

Variations from the Normal Course.—Even in the period of incubation there may be slight rises of temperature. In very young infants and in feeble, poorly nourished children this period may be prolonged. The stage of invasion may be comparatively short or unusually long. In the latter case, the initial rise of temperature occurs early, so that the eruption appears on the fourteenth day after infection. Sometimes the catarrhal symptoms are extremely severe. The nasal obstruction may be so great, especially in infants, that it causes dyspnea. The laryngitis may be so marked as to cause stenosis and a true croup may be suspected.

Variations in the Eruption.—Cases of measles without an eruption have been reported. Of course it is possible that the spots were very few and evanescent. I have seen a case in which a child was exposed to infection from another in the same family, and after 12 days had a rise of temperature to 102, and slight catarrhal symptoms. The blood showed the characteristic reduction in the relative percentage of lymphocytes, but no eruption appeared. In two instances I have seen children with a rise of temperature, the tonsillar spots, and what appeared to be typical Koplik's spots, who also failed to develop an eruption.

Prodromal Rashes.—These I have observed in only 1 per cent. of my cases. The true prodromal rash appears from one to three days before the true eruption, and is scarlatiniform, erythematous, or morbilliform in character. In many cases the true measles eruption appears to be beneath the skin, veiled as it were, 24 hours before it becomes distinctly visible.

The spots may be so large and numerous that they coalesce, forming *confluent* areas or patches. In certain regions, more especially on the face, forearms and buttocks, the eruption may become *hemorrhagic.* Such cases may run an otherwise normal course, and the prognosis is not necessarily grave. In such cases the spots and the pigmentation are visible for a very long time. When the spots are small and closely grouped, the appearance may be strikingly *similar* to that of *scarlet fever*, but other areas will always be found in which the eruption retains its true morbilliform character. On the chest and back, in parts in which sweating is more profuse, the eruption may be *vesicular* or *miliaria* like in character. This may also occur as a prodromal manifestation. In exceptional instances, the eruption may *spread* over the entire body *in* 24 *hours*. I have seen such a case in an infant one year old, in whom the disease ran an otherwise perfectly typical course. The *first spots* may appear in an *unusual location*, for example on the lower part of the body, and they may spread in an unusual way. They may be late in appearing and the eruption may have a cyanotic hue with a tendency to *recede*. These are the patients in whom the eruption is supposed to "strike inward." They are severe cases with circulatory disturbances. With an improvement in the action of the heart and a better peripheral circulation, the eruption reappears. I have seen a *recurrence* of the eruption in one case, one week after the original eruption, but it did not spread over the entire body. As a rule such recurrences are observed after 14 days, and seem to be more common in certain epidemics. Recurrences are associated with a new rise of temperature, and are similar in some respects to the relapses sometimes seen in typhoid fever. In some families one may note a resemblance in all the children affected, in the character, and distribution, of the eruption, and in the order in which the various parts are involved. In rare instances the eruption on the face may present a large number of *prominent papules*, so that the appearance is not unlike that of smallpox. Pustules may occur. The eruption may be bullous, urticarial, or erythematous in certain places. In those parts which are hyperemic, over eczematous or intertriginous patches, or parts which have been irritated, by mustard or burns, the eruption has a tendency to appear earlier.

Desquamation.—This is never so distinct as in scarlet fever, and may be very slight so as to be hardly noticeable. It is apt to be most distinct on the face, ears, and neck.

Complications and Sequelæ.—When we consider how exceedingly common this disease is, 95 per cent. of all children being attacked, complications are comparatively uncommon. This statement applies only to patients treated in their homes. On the other hand, in institutions, asylums and hospitals for communicable diseases, complications are much more frequent. Many of the children are in poor health, some have had a previous disease, which has lowered their resistance, so that cross infection is common. Children between one and two years are chiefly affected, and in different epidemics the frequency of complications varies greatly. This is probably due to a larger number of secondary infections, with streptococci, pneumococci, and influenza bacilli, at times when acute infectious catarrhs are prevelent. Measles seems to pick out the weak spot in the human organism. If a child has adenoid vegetation, or has previously had an attack of otitis media, the latter complication is likely to occur. If the child is subject to catarrhal infections of the respiratory tract, laryngeal and pulmonary complications may occur. If he has had gastro-intestinal disturbances frequently, a complicating colitis may occur. In a sense, measles acts as a test of normality, and since nearly every child is sooner or later infected, it is a very practical test.

Relative Frequency of Complications.—The following table gives an idea of the relative frequency of the commoner complications.

Complication	Landé, 192 hospital cases, per cent.	Herrman, 408 cases treated at home, per cent.
Pneumonia	21.8	4.5
Otitis media	13.5	3.0
Colitis	5.0	1.0
Respiratory	26.0	6.5
Digestive	21.0	5.0
Other infectious diseases	16.0	4.0

In 51 fatal cases observed by Holt[11] 88.2 per cent. died of pneumonia, 7.8 of ileocolitis, and 3.9 of membranous laryngitis.

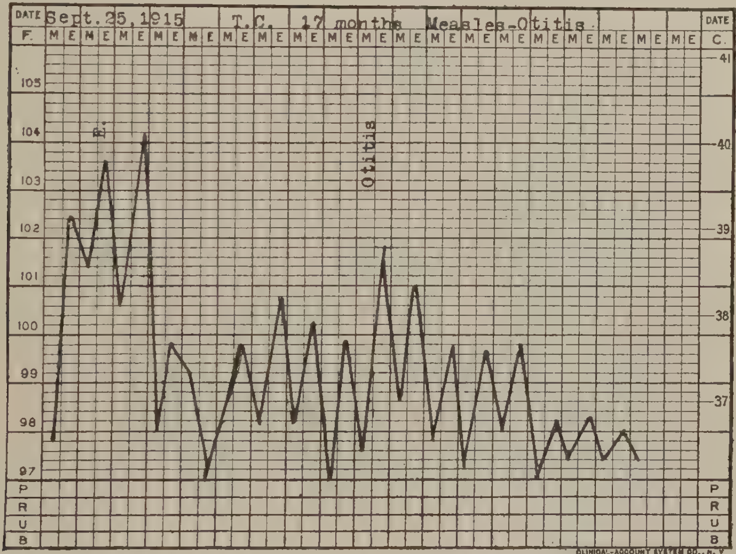

FIG. 56.—Temperature curve in a case of measles complicated by otitis media. Patient, seventeen months old.

In a small number of patients after the eruption has faded and the temperature has fallen, there may be another rise for a few days and still no complication develop. This may be due to pulmonary congestion. However as a rule a recurrence of fever or its failure to fall, indicates some additional lesion. The milder complications often appear singly, but in severe cases two or more complications are frequently present (Figs. 65–67).

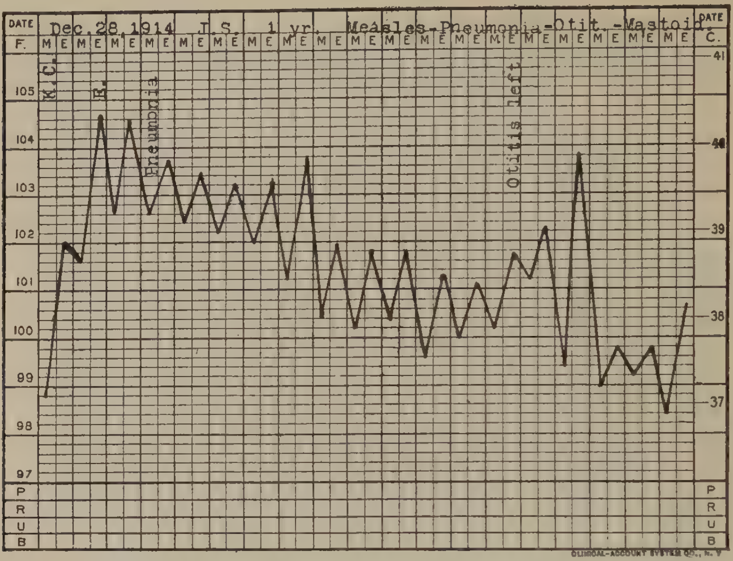

Fig. 57.—Temperature curve in a severe case of measles. Complicated by pneumonia. Otitis and mastoiditis. (Operated.)

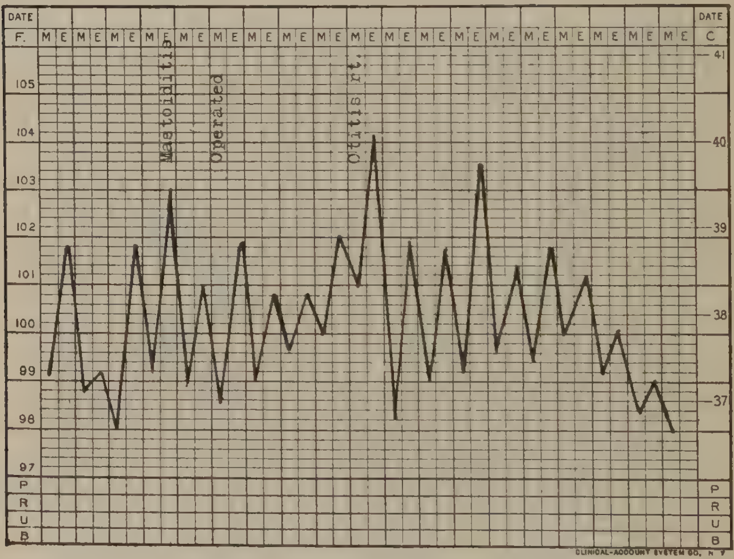

Fig. 58.—Continuation of Fig. 57.

Eyes.—In some patients the conjunctivitis persists. This is especially the case in children with the lymphatic tendency. It may be associated with a marginal blepharitis; corneal ulcers with photophobia and blepharospasm may develop. Some have a purulent conjunctivitis with pain, swelling and edema of the lids. Diphtheritic conjunctivitis is rare.

Nose.—In infants a marked swelling of the nasal mucous membrane may occur, which is associated with obstructed nasal breathing. This interferes greatly with nursing or bottle feeding. There may be little or no discharge. In other cases a profuse discharge is present, which causes an excoriation of the outlet of the nostril and the upper lip. If this is covered by an exudate, the appearance is strikingly similar to that in diphtheritic rhinitis. True diphtheritic rhinitis however may also occur. The nasal catarrh may spread to the eustachian tube and otitis media result.

Ear.—This complication is almost invariably accompanied by a rise in temperature (Figs. 56–58). Later the temperature curve is usually of the remittent type. The general condition, appetite, and sleep become worse. Pain in the ear may not be complained of or indicated, so that only an examination of the ear drum reveals the trouble. Inspection of the drum membrane shows that it has lost its normal pearly white luster, and it may appear reddened in certain parts, or it may be slightly bulging. If a simple catarrhal inflammation is present it may disappear spontaneously, if purulent it may perforate the drum membrane; but in all cases in which the fever persists, a paracentesis should be done, for the inflammation may spread to the mastoid cells or even to the lateral sinus and dura mater. A few cases go on to a chronic otitis media.

Mouth.—The more common conditions in the mouth, aphthous and parasitic stomatitis, are benign in character. At most they interfere with proper feeding. Ulcerative stomatitis occurs almost exclusively in institutional children, in those who are in unfavorable hygienic surroundings, or in those previously ill or suffering from some constitutional disease. It begins as a gingivitis, at the margin of the gums, particularly in children with carious teeth. When the resistance of the organism is below par, the ulcerative process progresses, and a gangrenous stomatitis may result. This begins as an infiltration of the mucous membrane and submucosa of the cheek; the deeper tissue becomes rapidly involved, so that the face shows an edematous swelling, in the center of which, a brownish-black necrotic spot is seen. This rapidly enlarges, breaks down and forms a foul smelling gangrenous mass. Fortunately, there is no severe pain. Death follows within a few days. Similar gangrenous lesions, noma, may occur in other parts of the body, more especially on the genitals. Gangrenous stomatitis simply represents a later and more advanced stage of the ulcerative form, and there is no sharp line between them. The fusiform bacilli of Vincent, and the spirochetes are associated with both processes. In the gangrenous form, they are found most abundantly at the boundary line between the healthy and the necrotic tissue (Fig. 59). Diphtheria bacilli may be found occasionally in such lesions, but they do not stand in any etiological relation. Children with measles may be infected with the Klebs-Löffler bacillus. The simultaneous presence of two infectious diseases, is of course more likely to lower the bodily resistance, and therefore the ulceration may go on to a gangrenous process. I have seen five cases of noma, four of which followed an attack of measles. Noma is more common after measles because the disease is so widespread, and because it is regularly associated with some changes in the oral mucous membrane. As previously mentioned, these ulcerative and necrotic lesions in the mouth are frequent in septic cases.

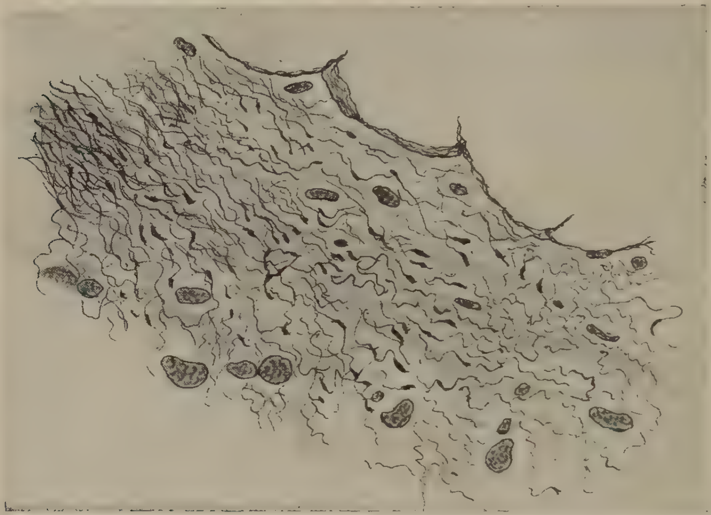

Fig. 59.—Noma. Section at the boundary line between the healthy and necrotic tissue. Showing the fine spirilla like wavy threads. To the left, toward the necrotic tissue thicker masses; to the right, toward the living tissue, more isolated. Some threads show a spindle like thickening. (Perthes.)

Larynx.—A catarrhal laryngitis may be one of the first symptoms of measles, especially in children who are subject to such attacks. The stenosis may be so marked that a membranous laryngitis is suspected. However even when there is an inspiratory retraction in the suprasternal and epigastric region, the symptoms usually subside and an incubation of the larynx is not necessary. The catarrhal laryngitis may persist, and hoarseness, even aphonia may result. In young infants this symptom may be a serious one, on account of the small caliber of the larynx, and the tendency of the inflammatory process to descend into the bronchi and lungs. These descending catarrhal inflammations are due to secondary invasion with streptococci, staphylococci, or pneumococci. True diphtheritic laryngitis also occurs and represents a very serious complication. The process may extend very rapidly, and diphtheritic antitoxin does not always seem to have the usual favorable effect in arresting the progress of the disease. I have seen diphtheritic laryngitis cause death in a patient with measles within 24 hours of the appearance of distinct laryngeal symptoms.

Bronchi and Lungs.—The pulmonary complications may be considered the most important, since they are the most frequent and cause the greatest number of deaths. About 10 per cent. of all cases have pulmonary complications, and about 75 per cent. of all the deaths in measles are due to pneumonia. Infants under two years are nearly 10 times as often affected as other children. In almost every fatal case of measles, some pulmonary changes will be found. The rapidly descending, so-called capillary bronchitis, is the most serious. This is much more common in infants, especially in those who are poorly nourished or rachitic. In some cases there is very little to indicate the impending danger, and the general condition of the child may change suddenly. He becomes pale and restless, the respirations are increased in frequency, the child becomes dyspneic, the wings of the nose dilate with each inspiration, and the accessory muscles of respiration are brought into play. The temperature rises (Figs. 60–62) and the pulse becomes rapid. Examination of the chest reveals the presence of fine more or less resonant râles, especially over both bases adjacent to the spinal column. Later the disease spreads, so that these râles may be heard over the greater part of both lungs, and only the upper anterior portion presents normal auscultatory signs. The smaller bronchi become filled with a mucopurulent secretion which interferes greatly with the proper aëration of the lungs. Although these symptoms are associated with a cough, the mucus is

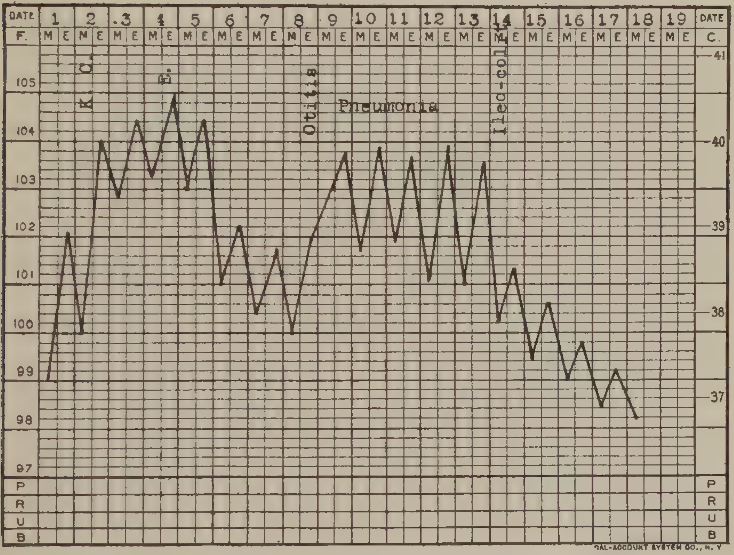

FIG. 60.—Temperature curve in a fatal case of measles complicated by otitis, pneumonia, and metastatic abscesses.

removed with great difficulty, and in infants and young children it is swallowed. In fatal cases the patient becomes apathetic, stuporous,

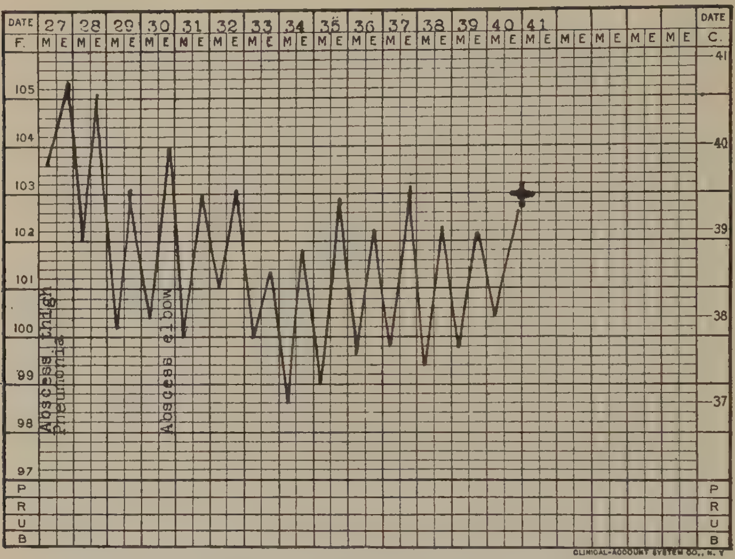

FIG. 61.—Same case as Fig. 60. Patient re-admitted to the hospital after an interval of nine days, with a second attack of pneumonia which proved fatal.

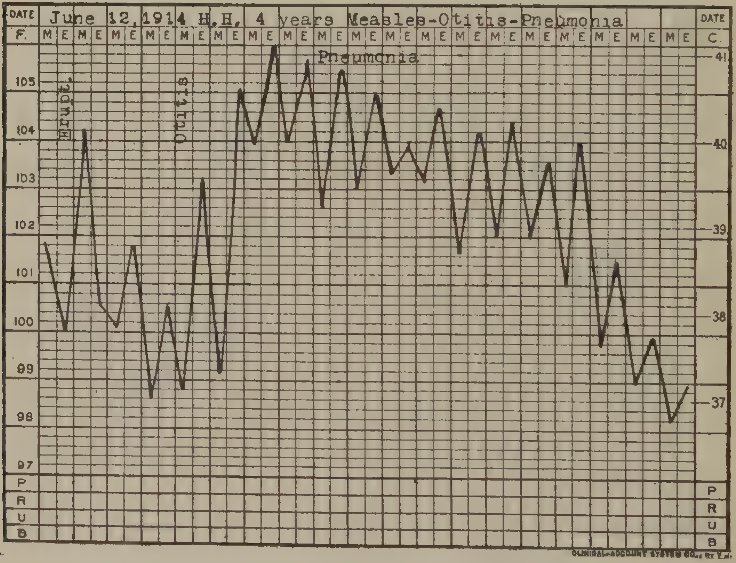

FIG. 62.—Temperature curve in a case of measles complicated by otitis and pneumonia.

and refuses nourishment. The heart becomes weaker, and death ensues, sometimes preceded by convulsions. In other cases the involvement of pulmonary tissue is not so rapid or widespread, only scattered areas in one or more lobes are present. In such patients the outlook is not so unfavorable. The fever is remittent or even intermittent in type, and on physical examination the symptoms of a bronchopneumonia are found, especially at the bases of both lungs posteriorly. At first a few crepitant râles are heard; then diminished pulmonary resonance and later bronchial breathing. These patients are also more or less apathetic and restless. The appetite is poor, and they have a persistent and very disturbing cough. In still other patients, the physical signs are more like those of a lobar pneumonia, and the fever is more continuous in character. In such patients the prognosis is more favorable. Pathologic examination of fatal cases shows, that the lobar involvement may result from the coalescence of a large number of small areas, for in other parts of the lung a combination of lobular and lobar involvement may be seen. A few cases are followed by a purulent pleuritis.

Heubner[10] has described a special and very severe form of pneumonia, which causes rapidly progressive necrotic changes in the lung tissue. In such cases the appearance of the eruption is delayed, and a characteristic pulmonary condition develops. This consists of an acute necrosis of pulmonary tissue, and a rapid development of bronchiectatic cavities, due primarily to a thinning and loss of resistance of the bronchial walls. Heubner believes that these necrotic changes are due to the measles poison itself, because they occur early in the disease; and compares them to the necrotic processes in the throat in scarlet fever.

Digestive.—The complications in the digestive tract are less common and less serious than the pulmonary. In all severe cases the lymphatic tissue of the gastro-intestinal tract is affected. Digestive disturbances may be present in the stage of invasion, in the form of vomiting or diarrhea. In most patients these symptoms disappear with the completion of the eruptive stage; but in a few they persist; the fever continues (Fig. 63) the patient complains of severe pain in the abdomen, and has loose, frequent, mucopurulent stools, often tinged with blood. If the disease progresses, the general condition suffers, and the central nervous system becomes affected; the tongue becomes dry, and the patient presents an appearance similar to that seen in a severe case of typhoid fever. If such gastro-intestinal symptoms are associated with an already existing pneumonia, as is not infrequently the case, the prognosis becomes very grave.

Nervous System.—Patients with a severe infection and very high temperature may have delirium. However this is not due entirely to the high temperature, for it may be present with a moderate fever, and absent with very high fever. Psychical disturbances may occur in convalescence. I have seen children who were previously bright, become apathetic, slow to respond to questions, after an attack of measles, and give the impression of being mentally backward. These symptoms disappear within a few weeks. These psychical disturbances are not peculiar to measles. They may also occur in the convalescence from other acute infectious diseases, but on account of the greater prevalence of measles, they are seen oftener after that disease. In infants with a spasmophilic tendency, convulsions may occur at the beginning of the disease. They are not necessarily of grave prognostic import. When convulsions occur later in the disease, they are more serious, as they are frequently associated with severe toxemia. A complicating meningitis is rare. I have seen a case of tuberculous meningitis develop in a child who had previously had a tuberculous infection. Serous, pneumococcus, and meningococcus meningitis have also been reported. In one patient I saw an acute encephalitis develop as a sequela of measles.

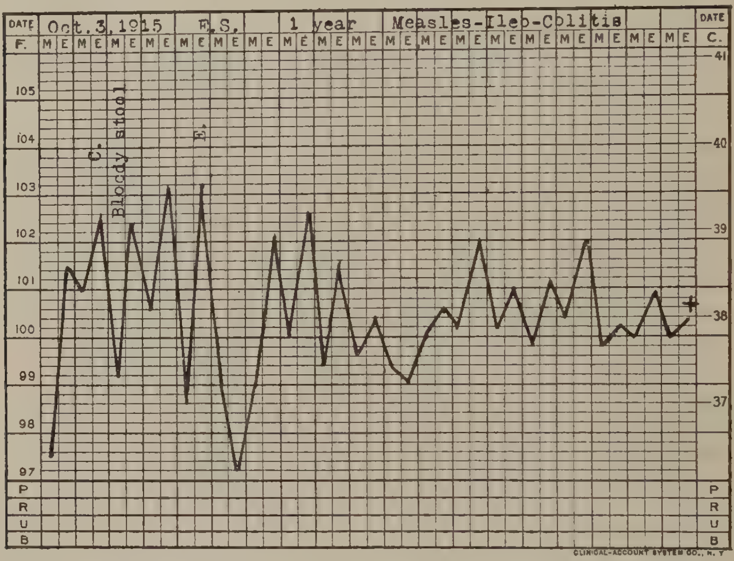

Fig. 63.—Temperature curve in a fatal case of measles. Complicated by ileocolitis.

Skin.—Chronic skin disease, such as eczema or psoriasis, may show a temporary improvement during an attack of measles. In children who are in poor physical condition, furunculosis may develop. Erysipelas, impetigo, and pemphigus, due to infection with the organisms associated with these conditions, is sometimes met with. The gangrenous processes have already been discussed. In tuberculous patients, tuberculides may be present, as small papules or nodules of a reddish-brown color, later showing a necrotic center.

Heart.—This organ is rarely affected. When involved it is usually the endocardium, with a permanent insufficiency of one of the heart valves. The pericardium and the myocardium are seldom attacked. Malignant endocarditis may occur in septic cases, and in the cases of necrotic pneumonia described by Heubner.

Kidney.—A small quantity of albumin may appear in the urine, but a true nephritis is very uncommon. When it does occur (I recently had such a patient under observation), it is of the hemorrhagic type, similar to that complicating scarlet fever. I have not seen pyelitis as a complication. A few such cases have been reported.

Combination with Other Communicable Diseases.—Measles may occur in a *vaccinated* child. In the two cases which came under my own observation, the normal development of the vaccination, was not disturbed. When measles and *varicella*, or *measles* and *scarlet fever* occur simultaneously, the course of each disease is not interfered with. When measles and scarlet fever occur together, the diagnosis may be difficult. The characteristic symptoms of both diseases must be present, in order to make the diagnosis certain. The presence of another case of measles or scarlet fever in the same family is of assistance. When two of the communicable diseases occur together, the prognosis is worse when the severer disease occurs later. Such combinations are of course more common, when both diseases are epidemic. Measles patients seem to be somewhat more susceptible to *diphtheria* infection than others. When such an infection occurs at the beginning of the disease, the course is apt to be more severe. A much more common combination is that of *measles* and *whooping-cough*, because in large centers of population, the two diseases are often prevalent at the same time. The combination is more serious, because both diseases have a tendency to affect the respiratory tract. Of 23 children in whom whooping-cough followed measles, 43 per cent. died; of 15 in whom scarlet fever followed measles 33 per cent. died, and of 15 in whom diphtheria followed measles 13 per cent. died (Comby[7]). This combination is much more serious in institutions, especially in those for infants, than in private practice. I have treated 10 cases of measles with whooping-cough in infants, in their homes, with only one death. In some the outlook seemed unfavorable, but they recovered. The following is such a case. An infant of eight months, artificially fed, and weighing 16 lb., contracted whooping-cough on August 14. On August 23 the patient had a rise of temperature, the following day catarrhal symptoms, and on August 27 an indistinct measles eruption appeared. He had a cyanotic hue, and a tendency to recede. In addition the patient had several convulsions. He received three injections of whooping-cough vaccin, which seemed to be of real benefit, and later made a complete recovery, without any pulmonary complication.

Tuberculosis.—It is a well-known fact that measles patients are predisposed to a tuberculous infection, and the onset of pulmonary tuberculosis may date from an attack of measles. In children who have a latent tuberculous focus, the attack of measles may activate the process. Tuberculous adenitis, especially of the cervical lymph-nodes may develop, or tuberculous lesions may appear in the bones or joints. Occasionally, the patient succumbs to a tuberculous meningitis. It is interesting to note that during an attack of measles, the von Pirquet reaction which had been positive, becomes negative. A few cases of pneumonia complicating measles, go on to the development of the chronic interstitial type, and pulmonary tuberculous may be suspected.

Diagnosis.—The diagnosis of measles should never be made from the appearance of the skin alone. Of all the manifestations, those in the mouth are the most characteristic and important. Koplik's spots are present in 90 per cent. of the cases, and I have never seen them in other conditions. However *all* the changes in the oral mucous membrane should be considered, for together, they are conclusive. A history of exposure 10 or 12 days previously is of value, as very few susceptible individuals escape infection. The change in the blood picture in the latter part of the period of incubation, is sometimes of value in the early diagnosis, but it can only be carried out in the hospital ward, and even there it will only be done when a primary case has previously occurred in the ward. In such cases the initial rise of temperature, in susceptible cases attracts the attention and the early oral manifestations are sought for.

Differential Diagnosis.—**Scarlet Fever.**—Measles and scarlet fever may occur in the same patient. In such cases the diagnosis may be difficult, and is certain only when the characteristic symptoms of both diseases are present. A history of exposure to these infections may be helpful. The measles eruption may be scarlatiniform in certain regions, but the characteristic morbilliform appearance will always be found in other regions. Important differential points are the presence of the eruption around the mouth and chin, the catarrhal symptoms and especially the oral manifestations. Measles attacks all the susceptible children in the family. Scarlet fever is much less communicable; only 25 per cent. of those exposed are infected.

Rubella.—If the patient is not seen at the outset, the differential diagnosis may be difficult. If the oral manifestations are indistinct or absent, as is often the case in young infants, the uncertainty may be still greater. In such cases the presence of measles in other children of the family, is of great assistance. The eruption of rubella is paler, and more pinkish in color. The fever and catarrhal symptoms are less marked, and above all the Koplik spots are absent. A temperature over 102 degrees is rare in rubella. The enlargement of the cervical, post auricular, and occipital lymph-nodes, occurs earlier and is more marked in rubella.

Small-pox.—This is now a rare disease with us. There are very few infants who are not vaccinated, and vaccination is compulsory for school children; so that in doubtful cases the probability that the disease is measles is much greater. The measles eruption resembles small-pox only when there are a large number of prominent papules on the face. The presence of a good vaccination scar, catarrhal symptoms, and the characteristic oral manifestations, serve to differentiate.

Typhoid and Typhus Fever.—Some years ago I saw a case of typhoid fever, in which the roseola spots were so numerous, that the eruption resembled that of measles; but the absence of distinct catarrhal symptoms, and the oral manifestations of measles, and the presence of an enlarged spleen, and later a positive Widal reaction, made the differentiation easy. Typhus fever is a comparatively rare disease in this country, at least in children. In this disease, the eruption is not distinct on the face at the beginning. There is an enlarged spleen, and the characteristic oral manifestations of measles are absent.

Influenza.—In the beginning of this disease the catarrhal symptoms and fever may suggest measles. The remission of 24 to 48 hours in the temperature, so common in measles is absent in influenza. Some cases of influenza are associated with a morbilliform eruption, but the Koplik spots are absent. When such cases occur in institutions, as these diseases always breed true, only other cases of the same disease will follow.

Syphilis.—The roseola of specific disease may in rare cases, resemble measles. Other symptoms of a specific infection, a positive Wassermann test, and the absence of high fever, catarrh, and the Koplik spots, serve to differentiate the two conditions.

Skin Diseases.—In my own experience, *sudamina, miliaria rubra,* are often diagnosed as measles eruptions. On the other hand, I have seen a true measles eruption, diagnosed as a heat rash. This has occurred more frequently in young infants, in whom, as has been already mentioned, the constitutional disturbance may be mild, and in whom the fever, catarrh, and oral manifestations are less marked. If there are other cases in the same family, the diagnosis is easier. The heat rashes persist for a longer time. *Erythema multiformi* also lasts for a longer time, it is not uniformly distributed over the body, and the catarrhal symptoms and Koplik spots are absent. *Intestinal and septic* rashes are sometimes morbilliform in character. The presence of symptoms pointing to these conditions, and the absence of catarrh, and the oral manifestations, serve to differentiate.

Vaccination, Antitoxin, and Drug Rashes.—In a small number of children, a morbilliform eruption follows vaccination. The injection of antitoxin (diphtheria, meningococcus) may be followed by a similar eruption. Antipyrin, quinin, iodides, balsams, morphine, occasionally cause such an eruption. The history of the case, the absence of catarrhal symptoms and the oral manifestations make the differentiation easy.

Diagnosis of a Pulmonary Complication.—I have seen a number of patients, in whom the presence of high temperature, prostration, increased frequency of respiration, and bronchial râles at the beginning of the disease, before the eruption appeared, which led the attending physician to make an incorrect diagnosis of pneumonia. These symptoms seem to be largely due to the toxemia. When the eruption appears, these symptoms tend to subside. One may sometimes be in doubt, as to whether the rapid breathing, and cyanosis is due to atelectatic areas or pneumonia, as the physical signs are similar. If the patient is given a warm bath followed by a cold douche, deep inspiration will be caused, the atelectatic areas are aerated, the breath sounds become more distinct over these areas, the pulmonary resonance returns, the breathing improves, and the cyanosis disappears.

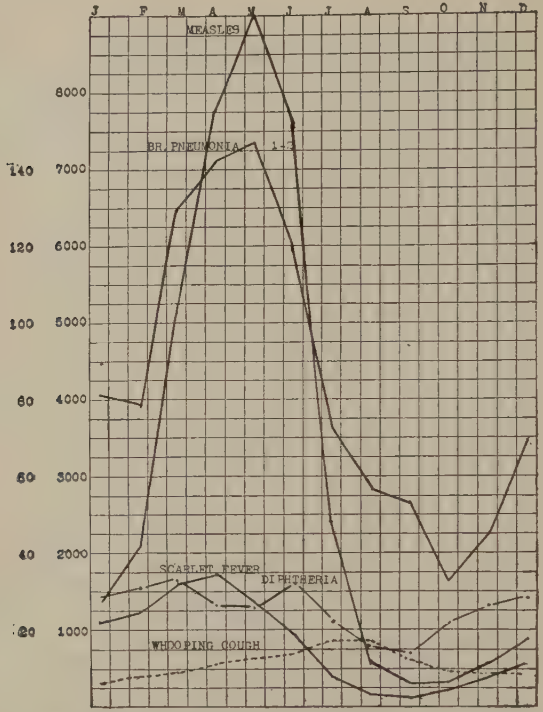

Fig. 64.—New York City, 1915—the morbidity from measles, scarlet fever, diphtheria, and whooping cough; and the mortality from bronchopneumonia between one and two years of age. Showing the parallelism between the morbidity from measles and the mortality from bronchopneumonia between one and two years of age.

	Measles	Scarlet Fever	Diphtheria	Pertussis	Mortality Broncho-Pneum. Bet. 1 and 2 Years
Jan.	1355	1094	1435	310	81
Feb.	2067	1201	1533	409	79
Mar.	5053	1592	1610	489	130
Apr.	7849	1731	1352	559	143
May	9088	1392	1341	637	146
June	7602	987	1634	701	120
July	2486	409	1120	806	73
Aug.	615	179	768	806	56
Sept.	270	147	722	630	54
Oct.	325	232	1081	493	33
Nov.	581	395	1293	468	45
Dec.	895	520	1390	463	70

Mortality and Prognosis.—Most of the statistics giving the morbidity and mortality from measles are unreliable. Depending on the regulations of the local Board of Health, from 25 to 50 per cent. of the cases are not reported. Many patients are never seen by a physician. A complete record of all cases would therefore reduce the mortality rate. On the other hand a large number of deaths which are recorded as due to pneumonia, especially those under two years of age are primarily caused by measles. Figure 64 shows the parallelism between the curves of morbidity from measles and mortality from bronchopneumonia between one and two years of age, in New York City in 1915. The curves of morbidity from whooping-cough, scarlet fever and diphtheria do not show this parallelism. The statistics of patients treated in hospitals, give a very high mortality rate, because a larger percentage are severe, and there is the added danger of cross infection.

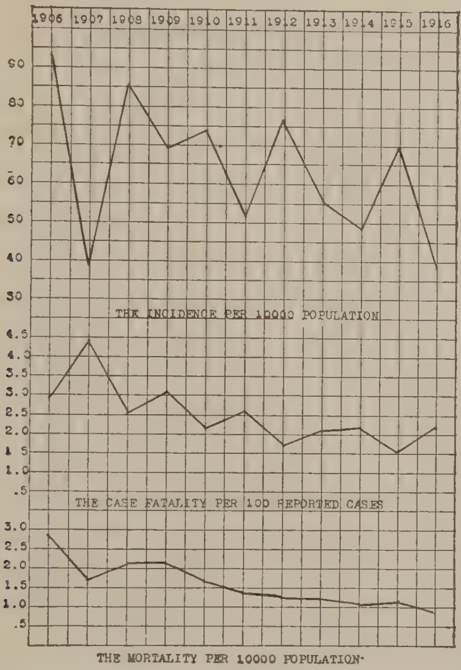

Fig. 65.—New York City, 1906–1916, the incidence per 10,000 population, of measles, the mortality per 10,000 population, and the case fatality per 100 reported cases.

	Incidence Per 10,000 Pop.	Mortal. Per 10,000 Pop.	Case Fatality
1906	92.8	2.75	2.9
1907	38.5	1.69	4.4
1908	85.6	2.17	2.5
1909	68.9	2.17	3.1
1910	73.8	1.63	2.2
1911	51.8	1.34	2.6
1912	77.0	1.25	1.7
1913	55.6	1.21	2.1
1914	48.4	1.05	2.2
1915	70.0	1.15	1.6
1916	38.5	0.87	2.2

Measles is responsible for a little less than 1 per cent. of all deaths in the temperate zone. During the 10 years from 1904 to 1913, the average annual death-rate per 100,000 population in the registration area of the United States, from measles was 10.2; and the average annual number of deaths was 9210. In the three years from 1912 to 1914, 471,742 cases of measles with 8331 deaths were reported from 33 states of the United States, giving a case fatality of 1.76 per cent. This I believe is very close to the true average mortality rate. The rate given by most authors is much higher. Holt[11] gives from 4 to 6 per cent.; Jürgensen, 6.1 per cent.; Heubner, 6.5 per cent.; Selter, 2.6 per cent.; Crum, for the city of Aberdeen, 3.3 per cent. I believe that most of these figures are too high for the mortality rate among the entire population, because they are based either upon a more severe set of cases, or upon an incomplete record of all cases which occurred. In large centers the morbidity and the mortality rate has been somewhat lowered during the last few years (Fig. 65). The average incidence per 10,000 population in New York City during the last 10 years has been 60.8; the average annual mortality per 10,000 population has been 1.45; and the average annual case fatality per 100 *reported* cases has been 2.46. As against the mortality rate of 1.45

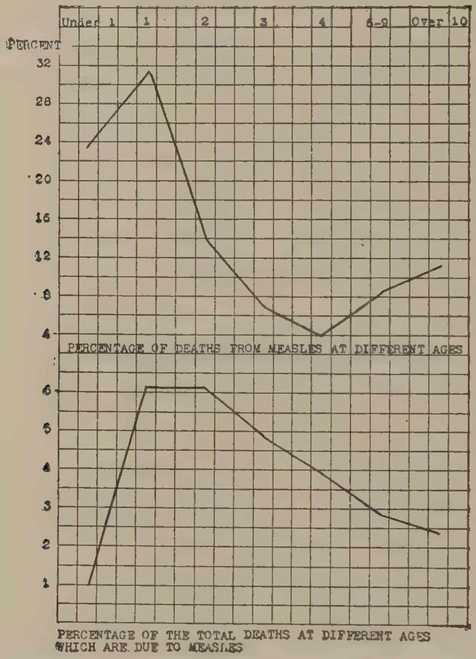

FIG. 66.—Showing the age distribution of 24,936 deaths from measles. United States registration area, 1910–1913, and the percentage of deaths from measles to the total mortality at different ages.

AGE	PERCENTAGE	PERCENTAGE OF TOTAL DEATHS, DUE TO MEASLES
Under 1 year	23.8	0.97
1 year	31.5	6.14
2 years	14.1	6.13
3 years	7.0	4.90
4 years	4.0	3.90
5–9 years	8.3	2.80
Under 10 years	88.8	2.40

per 10,000 population in New York City, in 1895 Paris had 2.6; London 5.9, Berlin 1.7; and Vienna 4.9 (Comby[7]).

Factors Which Influence Mortality.—*Age* (Fig. 66).—The largest number of deaths from measles occurs in children under two years of age, 55.3 per cent.; and 31.5 per cent. occurs between one and two years. In the first year of life, almost all the deaths occur in the second six months. After the third year, the number of deaths rapidly declines. Nearly 90 per cent. of the total mortality occurs in children under 10 years of age. Measles causes 2.4 per cent. of all the deaths in children under 10 years of age, and approximately 6 per cent. of all the deaths in children between one and three years of age. It is sometimes stated that the disease is more likely to run a severe course in adults. This is not true, at least in large centers where the disease is endemic. I have seen a number of adult patients, and in none of them did any complication occur.

Housing Hygienic Conditions.—The sanitary conditions surrounding the patient, seem to have a very distinct influence on the prognosis. This is very well illustrated by two groups of cases reported by Heubner,[10] which occurred in his district practice at Leipzig. In the first series there were 278 cases with a mortality of 10.3 per cent. These occurred in a district with very poor sanitary conditions. The second series occurred in the same district, but by that time a large number of the old houses had been torn down and replaced by more modern structures. The class of people occupying these was naturally somewhat better. In this series, there were 316 cases, with a mortality of 3.1 per cent., that is less than one-third the previous mortality rate.

Institutional and Home Treatment.—It is a well recognized fact, that the mortality is much higher in hospitals and other institutions, than in private practice. Holt[11] in 300 cases under three years which occurred in an epidemic of measles in an institution, had a mortality of 40 per cent. In another epidemic of 143 children under five years, the mortality was 35 per cent. At the Berlin Charité hospital, Henoch[12] had a mortality of 30.3 per cent. Between the years 1882 and 1894, according to Comby,[7] the mortality from measles in the hospitals for children in Paris averages 35 per cent. The marked difference in the mortality rate in institutions and in the home, is shown in a severe epidemic recently reported by Landé.[9] In a series of 192 cases, 47 patients were treated in the hospital with a mortality of 30 per cent.; 145 patients at home with a mortality of 3.4 per cent. Even if we make due allowance for the fact that the more severe patients would naturally be transferred to the hospital, the difference is striking. In a series of 408 patients whom I treated in their homes, the mortality was only 1.5 per cent.

Presence of Severe Complications, and Other Communicable Diseases.—This of course renders the prognosis less favorable. In those who have an intercurrent attack of scarlet fever, diphtheria, or whooping-cough, death is more likely to occur. In those patients who present a well-marked eruption, the prognosis is good; but if the eruption is indistinct, slow in appearing, of a cyanotic hue, or if it has a tendency to recede, the prognosis is less favorable, as such cases are often associated with pulmonary or circulatory disturbances. If the *fever* continues to be high after the eruption is completed, the outlook is less favorable, and a very high temperature at that time is so frequently due to the presence of some complication, that it renders the prognosis more serious. In a series of 161 hospital patients, Holt[11] found that the higher the maximum temperature, the greater the mortality rate.

	PER CENT. MORTALITY
Maximum temperature not over 102	0
Maximum temperature 102 to 103.5	7
Maximum temperature 104 to 104.5	16
Maximum temperature 105 to 105.5	40
Maximum temperature 106 or over	80

Prophylaxis.—The great difficulty in the prophylaxis of measles is due to the fact, that it is highly communicable before the eruption appears, at a time when in most instances, the disease is not even suspected. During this stage, the patient may mingle freely with others, and spread the disease broadcast. Prophylactic measures which begin with the appearance of the eruption are of no value.

Prophylaxis in the Home.—As the disease is a dangerous one for infants, and for weak and poorly nourished children, especial care should be taken, to guard these children against exposure, when other cases of the disease occur in the family, or in the same house. Except among the very poor and under unusual circumstances, the disease is not dangerous for children of the school age. As a rule the primary case is detected too late to prevent the other susceptible children in the family from being infected. However in families in which there are a large number of children, especially if one is an infant, it will be advisable to watch for the initial rise of temperature in the secondary cases, and to isolate them as soon as this is noted. The reporting of all cases is important, not only for statistical purposes, but because it renders possible early isolation of the secondary cases. In tenements the placarding of the door of the apartment, is not without value, because other mothers can then more readily prevent their own children from coming in contact with the children of the affected family. A strict isolation of the patient for five days is sufficient. After the eruption is completed and the temperature has fallen, the disease is not communicable. *Disinfection* of the room occupied by the patient is an unnecessary procedure. The infectious material is conveyed by the patient, not by the room or articles in the room. Its virulence is quickly lost by exposure to the air and sunlight, so that it suffices if the room is aired and cleaned. It may afterward be safely occupied by others.

Schools and Kindergartens.—Here the problem is more difficult. All children who have had an attack of measles, and who have been under the care of a physician, should receive a certificate (Herrman[6]). This is kept, so that when measles occur later in the same family, the child need not be excluded from school, and the susceptible and non-susceptible individuals will be definitely known, as in vaccination against small-pox. Teachers should be familiar with the early manifestations of the communicable diseases (Herrman[6]) so that those children that present suspicious symptoms, can be immediately isolated, and referred to the medical school inspector for further examination. When a case of measles occurs in one of the classrooms, the susceptible children should be regularly examined. It is practically impossible to exclude all children who have any catarrhal symptoms, for at certain seasons of the year, this would mean the exclusion of a very large percentage of all the school children. The regular weighing of all the children in order to determine the loss of weight in the latter part of the period of incubation, is difficult to carry out in school, and on account of the difference in clothing and the amount of food taken, would be unreliable. If it were possible to take the temperature of susceptibles regularly several times a day, it would be of value in detecting the initial rise, but this is hardly practicable in our public schools. My own plan has been to examine daily the mouths of all susceptibles, more especially at the time when secondary cases were due. This can be done very quickly, and as soon as the tonsillar or Koplik spots are seen, the children are excluded from school. I do not think that it is necessary to close the school or even one classroom, as a very large percentage of school children, at least in large centers of population, have had an attack of measles. However in kindergartens, day nurseries, and other places where there are a large number of infants and very young children, it may be advisable to close for a time. The exclusion of the other susceptible children in a family in which a case has occurred, need not be for more than 14 days, for by that time there will be at least an initial rise of temperature to indicate that the child has been infected. If accurate records were kept, it would only be necessary to exclude these children from the seventh day after the occurrence of the primary case. If the condition of the patient warrants it, he may return to school one week after the appearance of the eruption. An exclusion for three weeks, as is common in many cities is unnecessary.

Hospitals and Other Institutions for Children.—In taking the history, it should be noted whether the child has had an attack of measles. All children should be placed in an observation ward for 14 days, before being admitted to the regular ward. Under no circumstances should other children be allowed to visit the wards. As far as possible each child should be isolated or separated from its neighbors, and for this purpose it is not necessary to have the "box" system or even permanent partitions. For some years, I have had linen sheets attached to the sides of the cribs, and have found that this method is sufficient to prevent contact or cross infection, through coughing and sneezing. On admission and daily thereafter, the mouths of all patients should be examined. If a case of measles develops in the observation or regular ward, it should be isolated immediately, and the remaining patients examined for the early manifestations. The date is noted, and the fact that from eight days later, secondary cases are to be looked for. In this early detection the differential white blood-cell count is valuable; but if the child is isolated so soon as the initial rise of temperature occurs, the further spread of the disease can be prevented. It is a decided advantage if hospitals and institutions for children, have facilities for treating the cases of measles which occur in their own wards, so that it is not necessary to send the patient to a hospital for communicable diseases. There are of course exceptional cases in which this must be done, but the danger of cross infection must be remembered. Simple uncomplicated cases of measles, should be separated from those with pneumonia, colitis, and other complications. At home even in the poorest surroundings, many of the dangers can be avoided. The mother, though untrained, can give her child individual care and attention. Even in our best hospitals, one nurse must take care of a number of children.

In hospitals for communicable diseases, all patients in whom the diagnosis of measles is not certain, should be kept in an observation room for a short time. I have known of patients with rubella who were placed in the measles ward, and contracted measles. Instead of being sick for a few days, they remained at the hospital for four weeks or more. This adds an unnecessary expense to the community. As children are sent to the hospital for communicable diseases, after the eruption has appeared, the stage of greatest infectivity has passed, and the damage has been done already.

In hospitals for the treatment of measles patients, or in institutions in which measles is prevalent, it is advisable to administer an immunizing dose of diphtheria antitoxin to each patient. If the Schick test is made, only those giving a positive reaction need be injected; but such injections must be repeated every two weeks if the patient remains in the institution.

Immunization against Measles.—(1) *Immunization with the Serum of Patients Convalescing from Measles.*—The method of prophylactic inoculation is briefly as follows: One week after defervescence from measles, that is, about 10 days after the appearance of the eruption, from 60 to 80 c.c. of blood is withdrawn from the vein of an otherwise healthy child over three years of age. The serum is separated, a small quantity of tricresol is added as a preservative. If possible, the serum of several patients is mixed. For prophylactic inoculation from 3 to 6 c.c. of the serum is injected intramuscularly not later than the fourth day of the incubation period. The chief objection to this method is that it confers a passive immunity which lasts only about eight weeks, and that this immunity is not absolute for that length of time. The method has only a limited application, namely, in asylums, and in other institutions for the care of infants and young children, where, when a case of measles occurs, the other children may be given prophylactic injections.

2. *Immunization with the Virus from Patients in the Active Stage of Measles.*—In April, 1914, I began to inoculate against measles, the method depending on the following facts: Seventy-five per cent. of the deaths from measles occur in infants under two years of age, therefore any method of immunization which aims to control or eradicate the disease, must be employed in early infancy on all or nearly all children. Infants whose mothers have had measles, are relatively immune to the disease during the first five months of life. In measles the infectious material is regularly present in an active form in the nasal discharge from 24 to 48 hours before the eruption appears. It is not necessary to isolate and identify the infectious material, or to obtain it in pure culture, in order to immunize against the disease. In measles, as it occurs in practice, the infectious material is conveyed usually from the nasal mucous membrane of the patient to the nasal mucous membrane of the child infected. The immunizing inoculations follow the same path. The nasal mucous discharge of patients, free from other diseases, is taken from 24 to 48 hours before the appearance of the eruption. It is mixed with a small quantity of normal saline solution, and bacteria and other extraneous material removed by separation after centrifugalization. A little tricresol is added as a preservative. A few drops of this solution are applied to the nasal mucous membrane of the infant to be immunized. Only healthy infants between four and five months are inoculated. The method endeavors to convert the temporary relative immunity into an immunity which persists at least during the first few years, that is during the period when the disease is most dangerous. I have found that the best results are obtained when there is some reaction following the inoculation. This consists of a slight rise of temperature on the eighth to the sixteenth day; occasionally a few spots on the face or body. It is therefore advisable to inoculate as near as possible to the end of the fifth month. In 165 inoculations, I have not had a single case which exhibited any unfavorable symptoms. Of the 165 who were inoculated in the fifth month 75 have been followed from four to eight years. Of these 70 have remained free from measles, although 45 have been directly exposed to infection, 17 by contact with infected children in their own family, and 28 by contact with children living in the same house who developed measles. In 84 of the 165 inoculated, I observed a definite reaction, and none of these contracted the disease. Thirty-six of those inoculated, with a reaction following, were re-inoculated after an interval of at least six months, and none developed the disease.

General Treatment.—In the treatment of a disease which is exceedingly common, which affects chiefly infants and young children, and which usually runs a benign course, it is but natural that untrained advisers should play an important part. As the vast majority of patients recover, these take upon themselves the credit. Through their influence, certain methods of procedure have become so deep rooted that the trained physician often finds it difficult to introduce innovations. There are three essentials upon which these grand-mothers and neighbors insist. The room must be pitch dark, the windows must be tightly closed, the patient must be wrapped in blankets, and under no circumstances must any water come in contact with the surface of the body. Intelligent physicians now believe that the sick room should be cheerful and that the patient should be made as comfortable as possible. To this end a light airy room is chosen, or if the circumstances permit two rooms, so that one can be thoroughly aired, while the other is being used. If there is strong sunlight, the bed is placed so that the patient does not face the bright light, or the shade is partly drawn. It is not necessary to have the room dark. I have frequently seen shawls fastened against the windows so that not a ray of light could enter. This only serves to depress and frighten the patient, and makes it difficult to ventilate the room properly. The window in the patient's room, or in the adjoining room should be left partly open. If steam radiators are used in winter, a small vessel of water should be attached so that the air is kept moist. It is not necessary to smother the child in blankets or feather beds, which simply add to his discomfort. The covering can be arranged so that there is no undue exposure. Water should be used freely externally to reduce the temperature, to stimulate respiration, and internally to supply a proper amount of fluid to the tissues. If the frequent application of water causes eczema, oil, or cocoa butter may be used to protect the skin. A mentholated ointment may be used to relieve itching. High temperatures are best reduced by hydrotherapeutic measures. The patient may be sponged with alcohol and water, or in more severe cases cold packs, douches or baths may be indicated. The restlessness is relieved by the application of cold compresses to the head, and the administration of from 1 to 5 gr. of phenacetin every three or four hours, depending on the age of the patient. The *feeding* may sometimes be difficult, all nourishment may be refused. In such cases at least water must be given, if necessary per rectum. Where there is a tendency to vomiting, skimmed milk is preferable to whole milk, and if this is distasteful, a little cocoa or chocolate flavoring may be added, or malted milk may be tried. When the temperature begins to fall, thin gruels, eggs, and broths are added to the diet.

Special Treatment.—Eyes, Ears, Nose and Throat.—The mild conjunctivitis which is regularly present is treated with a solution of boric acid. For the subacute cases a 10 per cent. solution of argyrol is applied twice a day, or the glycerite of tannin may be used. Marginal blepharitis is treated with a 1 per cent. yellow oxide of mercury ointment, and the matting together of the lids may be prevented by applying a boric acid ointment. If corneal ulcers develop a few drops of a solution of atropin sulphate are instilled, and an oculist should be consulted.

The routine use of urotropin may possibly have some effect in preventing the involvement of the middle ear. A simple catarrhal otitis media may be treated with the local application of heat; but if the fever persists, if there is an injection or bulging of the drum membrane a paracentesis should be done.

The *rhinitis* which is regularly present usually requires nothing more than cleansing with a boric acid solution, or the instillation of liquid albolene. If the outlet of the nostril and upper lip are irritated by the discharge, the parts are protected by a bland ointment. If the nasal obstruction becomes marked, an ointment or solution containing adrenalin chlorid is useful, and for subacute rhinitis a 10 to 20 per cent. solution of solargentum is applied twice a day. *The mouth* and teeth should be kept scrupulously clean, especially in poorly nourished sickly children, with low resistance; for in such patients, ulcers easily develop and spread. Besides the mechanical cleansing, a mild antiseptic wash may be used. If sprue is present, a 1 per cent. solution of formalin is applied to the affected parts. In ulcerative stomatitis, potassium chlorate is given internally in doses of 1 gr. every two hours, and a solution of equal parts of tincture of iodin and glycerin is applied locally. A solution of permanganate of potash may be used as a deodorizer. If the lesions become gangrenous, injections of neosalvarsan are given intravenously, and in some cases have given good results. If it fails to control the progress of the disease, the necrotic tissue must be excised and the base touched with the Paquelin cautery.

In tonsillar and laryngeal *diphtheria*, large doses, from 10,000 to 20,000 units of antitoxin should be given immediately, in urgent cases intravenously. The effect is often not as striking as in simple, uncomplicated cases of diphtheria.

Respiratory Tract.—If the laryngitis is severe, it is treated with hot drinks, warm compresses around the neck, and inhalations of tincture of benzoin. When the stenosis becomes marked, it may sometimes be relieved by giving a hot bath at 104 degrees for 15 minutes. If the cough is dry and very distressing, small doses of antipyrin or codein may be given. In the cases of so-called capillary bronchitis, in which the smaller bronchi become filled with a tenacious mucus, the use of the mustard pack often gives great relief. According to Heubner[10] it is prepared as follows: One pound of fresh mustard flour is stirred in 1 qt. of hot water. A towel large enough to encircle the body from the neck to the soles is dipped into the mustard water, wrung out, and applied to the patient. He is then covered with a dry blanket, and allowed to remain in these coverings for 15 to 20 minutes, that is until the skin becomes distinctly red. The coverings are then removed, the surface of the body is quickly sponged, in order to remove the remaining particles of mustard flour, and the child is wrapped in another towel, which has been dipped in plain hot water. In this he remains for one hour, during which time the hyperemia which has been caused by the mustard water continues. The body is then dried and covered by blankets. This procedure is carried out once a day, and if it does not produce a reaction it is discontinued. Broncho and lobar pneumonia are treated as in other conditions. The details will be found in another section of this work.

In those patients in whom the eruption fails to come out distinctly, and has a tendency to recede, a warm bath of plain or mustard water, should be given. If the eruption is also of a cyanotic hue, this bath may be followed by cold douches, which cause deep inspiration, expansion of the lungs, and improvement in the circulation. Patients with a high temperature, delirium and dry tongue, in whom the pulse is good, are also benefited by cold douches, packs, or baths. In such patients it is advisable to give a stimulant before and after the bath. In patients who have a poor pulse, a reliable preparation of digitalis is used, and when dyspnea and cyanosis are marked, inhalations of oxygen will at least make the patient a little more comfortable. If the bronchitis persists after convalescence, guaiacol should be given; and if there is an interstitial pneumonia or if pulmonary tuberculosis is suspected, life in the open air and sunshine should be advised.

Intestinal Tract.—A slight looseness of the bowels sometimes occurs in the prodromal stage, and needs no special treatment. Constipation is best relieved by enemata; for if laxatives are given, they may cause a looseness of the bowels, which it is difficult to overcome. If ileocolitis develops, the diet is restricted to skimmed milk and broths, small doses of opium are given after the bowels have been emptied, and the lower bowel is irrigated, after a cleansing enema, with a 1 per cent. solution of tannic acid. Tympanites is best relieved by giving a hypodermatic injection of 3 to 5 minims of pituitrin, followed in 15 minutes by the introduction of a rectal tube.

Nervous System.—High fever, delirium and a dry tongue are best treated by the use of cold packs or baths, if the pulse is of good quality. Cold compresses are applied to the head, and small doses of phenacetin are given. If the patient has convulsions, a lumbar puncture with the evacuation of 10 to 20 c.c. of spinal fluid, often gives relief.

In the milder cases, it is not necessary for the patient to remain in bed for more than five to eight days, and if the weather is favorable they may go out two or three days later. Patients with persisting catarrhal symptoms, or complications, will require a longer time; but children who have had an ordinary attack, may be allowed to return to school after a week or 10 days, as at that time there is no danger of infecting others. A cleansing bath should be given daily after the eruption has begun to disappear, and if there is dryness of the skin, desquamation or itching, the body may be anointed with oil or cocoa butter.

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CHAPTER CLVI

RUBELLA (GERMAN MEASLES—RÖTHELN)

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Rubella must have been considered a very important disease by American pediatrists 30 years ago, for in Keating's "Cylopedia of Diseases of Children," only eight pages are devoted to measles and 18 to rubella.

Rubella is now universally recognized as a distinct and separate disease, for an attack does not protect the individual against measles, or scarlet fever, and these diseases in turn do not protect against rubella. I have seen several children, who at different times had these three diseases. When a case of rubella occurs in a family or an institutions, it always causes other cases of rubella, in other words, it breeds true.

Etiology.—The character of the infectious material is absolutely unknown, but it is highly probable that it is in many respects similar to that of measles. With the assistance of Doctor Lenz, I have made blood cultures, just before and just after the appearance of the eruption, using different media, including those used by Tunnicliff in measles, but the cultures always remained sterile. Hess[1] also failed to cultivate any organism from the blood; and experimental inoculations into monkeys failed to produce the disease.

Susceptibility and Immunity.—The disease is much less communicable than measles. About 30 per cent. of all susceptible children who are exposed are infected. This low degree of communicability is due, I believe, to the fact that the catarrhal symptoms are much less marked than in measles, the coughing and sneezing much less severe, and therefore particles of infectious mucus are less frequently conveyed to other children. In addition very intimate contact is required, and the period of infectivity is shorter than in measles. I have noticed that when rubella occurs in a classroom, not more than one-fourth of the children are infected. In a series of cases which I had an opportunity of observing in a recent epidemic, 70 susceptible children were exposed to infection, and only 24, that is 34 per cent. contracted the disease.

One attack usually protects the individual for life. Box[2] in 850 cases treated in his hospital practice, observed a second attack in 3 per cent.; but unless one has himself seen both attacks, the diagnosis should be made with hesitation, as similar eruptions may be due to intestinal disturbance, drugs, etc. In doubtful cases a history of exposure to infection is necessary.

Age and Seasonal Incidence.—Infants under six months are rarely infected. In a series of 63 cases which I recently observed the ages were, 1 year, 7 cases; 2 years, 8 cases; 3 years, 6 cases; 4 years 6 cases; 5 years, 13 cases; 6 years, 6 cases; 7 years, 6 cases; 8 years, 4 cases; 9 years, 3 cases; 10 years, 2 cases; 13 years, 1 case; 17 years, 1 case. In a series of 138 cases, Schick[3] had 13 at 2 years; 41 from 2 to 5 years; 62 from 5 to 8 years; 18 from 8 to 10 years; and 4 from 10 to 13 years. It will thus be seen that the disease is most common at a little later age than measles. This is probably due to the fact, that as rubella is less communicable than measles, a certain number of children escape infection at the first exposure, and contract the disease at a second exposure later in life. Adults of all ages may be infected. The number of cases of rubella, gradually increases from January, and usually reaches its maximum in May (Fig. 67). In epidemic years, which occur at intervals of three or four years, there is a sudden rise in March, and the maximum is reached in April or May. The number of cases rapidly diminishes, and the lowest point is reached in September or October. This corresponds very closely with the seasonal incidence of measles, so that it is highly probably that the same factors influence the prevalence of both diseases.

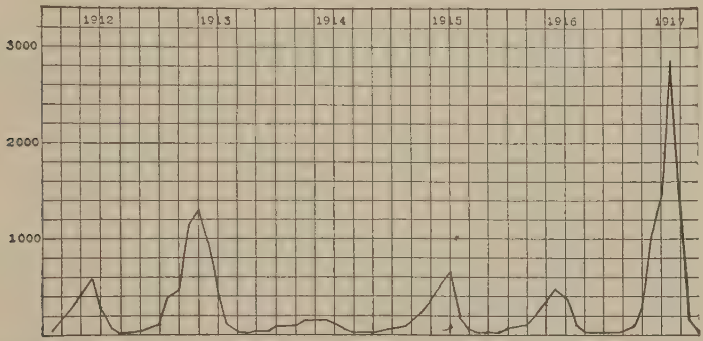

FIG. 67.—The seasonal incidence of rubella, New York City, 1912–1917.

	1912	1913	1914	1915	1916	1917
Jan.	51	421	69	92	86	108
Feb.	120	448	85	150	113	285
Mar.	298	1143	166	213	225	1085
Apr.	421	1311	150	395	346	1468
May	587	973	174	509	475	2860
June	285	493	129	636	395	2279
July	71	105	54	196	132	162
Aug.	11	18	17	40	29	33
Sept.	11	12	16	25	14	
Oct.	26	20	11	20	11	
Nov.	72	25	20	15	17	
Dec.	102	72	47	50	26	

Mode and Period of Infection.—The infection in rubella as in measles, takes place by direct contact with a patient, and in rubella this contact must be very intimate. There is no evidence that it can be carried by a third person or by inanimate objects. The mucus from the nose and throat probably contains the virus, and the infectious material is conveyed in coughing and sneezing, possibly also in talking. The disease is probably transmitted only in the catarrhal stage, from 48 hours before to 24 hours after the appearance of the eruption. After the eruption is complete, the disease is no longer communicable.

Incubation.—The period of incubation is variously given by different authors. Pospischill believes that it is usually 14 days. Henoch gives the average as 17 days. In a small series of patients in whom Schick[3] was able to determine this period with accuracy, it was from 15 to 23 days. Most authors give from 16 to 21 days. In a recent epidemic in New York City, I had an opportunity of determining the period of incubation with a fair degree of accuracy in 33 cases. It was 11 days in 2 cases; 12 days in 3 cases; 13 days in 5 cases; 14 days in 10 cases; 15 days in 4 cases; 16 days in 3 cases; 17 days in 4 cases; 18 days in 1 case; and 19 days in 1 case; so that the largest number occurred 14 days after infection. The following series of cases which occurred in two families occupying adjoining rooms, illustrates the uniformity in the period of incubation, and also furnishes strong evidence that the disease is only communicable during the short catarrhal stage. The one family consisted of three children, aged seven, five, and one years; the first child had the eruption on March 4, the second on March 18, and the third on March 31. The last then infected the two children of the other family, and these showed the eruption on April 17. Four of these five children had had measles previously.

Symptomatology.—As a rule there are no distinct symptoms in the period of incubation. The first manifestation is usually a slight rise of temperature. There may be headache, indisposition, a loss of appetite, and sometimes sore throat. Vomiting occurs in only about 1 per cent. of cases at the onset. The period of invasion is brief, or it may be entirely absent, and the eruption itself may be the first manifestation of the disease to attract attention. Mild catarrhal symptoms may precede the appearance of the eruption. The oral mucous membrane does not show any of the manifestations so characteristic of measles, and I have never observed the film on the gums or Koplik spots. Forchheimer[4] has described an exanthema on the palate, which consists of minute bright red spots or fine points on the uvula and soft palate, occasionally also on the hard palate. They are seen only during the first 24 hours of the disease. In a recent epidemic, these spots were seen in only 25 per cent. of the patients, while a sore throat was more frequently complained of. There is usually a slight conjunctivitis, a slight increase in the nasal secretion, and a little cough, but the tongue shows no changes, and the appetite and bowels are seldom disturbed.

Eruption.—This is the most prominent symptom, and usually appears first on the face, including the circumoral portion. The individual spots are at first pin head in size and of pale rose-red color. They increase somewhat in size, but remain uniform in contour. They are not as distinctly papular as the spots in measles, and are not as close together as those in scarlet fever. The eruption spreads rapidly over the body, involving in turn, the trunk and extremities, so that it is usually completed in 24 hours. The extensor surfaces of the extremities are more markedly affected. Sometimes the eruption spends itself before reaching the distal parts of the extremities. It begins to fade quickly, first on the face, so that it is seldom visible for more than three or four days. There is little or no desquamation.

Lymph-nodes.—There may be slight swelling and pain in cervical, or occipital nodes, even before the appearance of the eruption. The other lymph-nodes, axillary, epitrochlear, and inguinal may also be palpable, but the most characteristic are the occipital and post-auricular. This enlargement of the nodes may persist for some time after the disappearance of the eruption. I have not found an enlargement of the *spleen;* and it must be remembered that occasionally a palpable spleen may have been present, before the child contracted rubella. The *urine* is free from abnormal constituents, and gives a negative diazo reaction. According to Hildebrandt and Thomas, there is a leukopenia, most marked on the third day of the disease; the polynuclear leukocytes are diminished, and the lymphocytes increased in number. Hess[1] also found a lymphocytosis just preceding the appearance of the eruption. In convalescence there is a slight increase in the leukocytes.

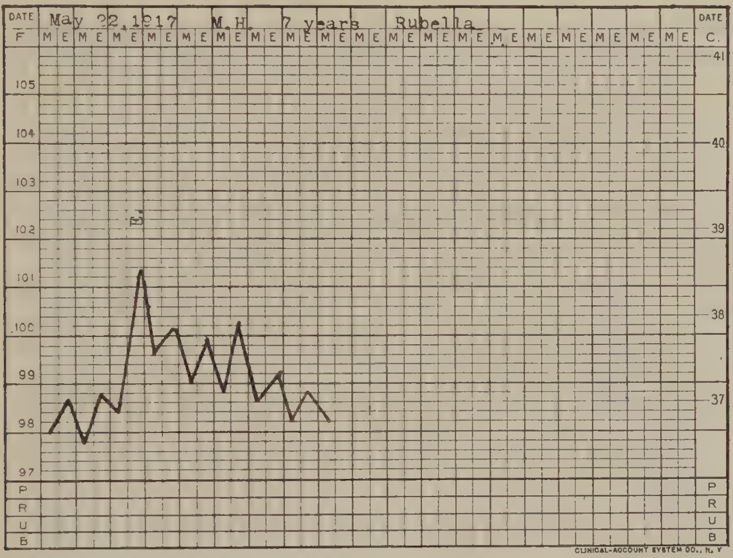

FIG. 68.—Temperature curve in a case of rubella. Patient, seven years old.

Fever.—There is no rise of temperature in the period of incubation, but there is often a slight rise on the day preceding the appearance of the eruption. The temperature usually reaches its maximum on the day of the eruption, and is rarely over 102 degrees (Fig. 68) and usually between 100 and 101 degrees. In rare instances no rise of temperature has been noted. In a series of 25 cases in which the temperature was taken regularly, I found it under 100 degrees in two; from 100 to 100.5 degrees in nine; from 100.5 to 101 degrees in seven; from 101 to 101.5 degrees in three; from 101.5 to 102 degrees in two; and over 102 degrees in two cases. The temperature returns to the normal in the course of two or three days, showing morning remissions.

The **pulse** is not distinctly increased in frequency, and is in proportion to the temperature.

In a small percentage of patients the disease, or one or more symptoms may present changes from the typical course. In a few, fretfulness, headache, diminished appetite, or sore throat, may be present before the eruption appears. Catarrhal symptoms may also be present at this time, as well as the enlarged and painful cervical, occipital and mastoid lymph-nodes already mentioned.

Irregularities in the Eruption.—There may be very few spots and these may be indistinct, so that the diagnosis is only possible if other cases have occurred in the same family. If it is a primary case, with very slight constitutional disturbance, it may go entirely unrecognized. In other patients the spots are very numerous, so that in certain regions they may coalesce. The first spots may appear on the arms, chest, or back, and the eruption may present a different appearance in different parts of the body. However, I believe that if the eruption is seen from the *beginning*, it will be found to have a distinctly *morbilliform* character. In *all* the patients whom I saw in a recent epidemic of rubella, the eruption was of this character. *Later*, if the spots are very numerous, and very closely grouped in certain regions, the resemblance to the eruption of scarlet fever, may be great. The question of scarlatiniform eruptions, will be discussed under Filatow-Dukes' disease. Hemorrhages into the skin occur occasionally.

Complications.—Either the complications described by some of the earlier writers, were due to an incorrect diagnosis, or the disease has become milder in character. In a child that had been previously ill, the disease might run a more severe course, but I have never seen a patient whom I considered dangerously ill. In a few otitis media followed the attack. The enlarged nodes do not suppurate. Other authors have met with stomatitis, paralyses, pneumonia, enteritis, and nephritis; but it is possible, that some of these cases were measles or scarlet fever. Rheumatic pains in the joints are not uncommon, Box[2] found them present in 3 per cent. of his cases. The joints of the hand and fingers are more frequently affected, and the pain lasts for three or four days. Cardiac complications do not occur. In one patient, I observed two *recurrences* of the eruption after an interval of 14 days.

Diagnosis.—If the patient is seen from the beginning of the attack, the differentiation from *measles* is not difficult. The absence of high fever, marked catarrhal symptoms, and the characteristic oral manifestations suffices. In infants under eight months with measles, these symptoms may be very mild, and in such cases it may be difficult to decide whether the child is suffering from a mild attack of measles or from rubella. As these diseases always breed true, the presence of another case in the same family, or ward, is of great assistance. If the case is one of measles, the other susceptible children are almost certain to contract the disease; rubella is much less communicable. A history of a previous attack of measles, practically rules out a second attack. If the patient is seen after the eruption is complete, the difficulties may be much greater. At this stage in measles, the temperature has usually fallen, and the oral manifestations may be slight or absent. In typical cases, the eruption of rubella is of a paler color, the individual spots are smaller, and less distinctly papular, and the eruption spreads more rapidly over the entire body. The desquamation is less marked and no pigmentation of the skin remains. An absolute diagnosis should not be made from the appearance of the skin alone. The period of incubation, to the appearance of the *initial fever*, is shorter in measles; the enlargement of the cervical, occipital and mastoid nodes is not so early, or so distinct. The diazo reaction is positive in measles, and negative in rubella. In measles in the prodromal stage there is a lymphopenia, in rubella a lymphocytosis. If the patient has had a tuberculous infection, the von Pirquet reaction will remain positive in rubella, but will become negative during the attack in measles.

Scarlet Fever.—If the patient is seen from the *beginning* of the attack, the eruption in rubella, will be found to be morbilliform in character. At a later stage, the spots may be so close together in certain regions, that the eruption in those places resembles that of scarlet fever. This question will be more fully discussed, under Filatow-Dukes' disease.

Intestinal, antitoxin, and drug rashes may resemble that of rubella, but the history of the case, the absence of catarrhal symptoms, and swelling of the lymph-nodes, usually suffices for differentiation.

Prognosis.—As has been stated, severe epidemics, cases with grave complications, and even death have been reported, but I have never seen a patient that did not entirely recover, or that was at any time in an alarming condition.

Prophylaxis and Treatment.—As the disease is much less communicable and less dangerous than measles, isolation is not so important. The primary cases are seldom recognized sufficiently early, to prevent the infection of others. Secondary cases in a family, ward, or school room, may be detected early, if the susceptible children are carefully watched, and the initial rise of temperature, the early enlargement of the cervical, occipital, and mastoid nodes, and the presence of Forchheimer's spots on the palate are looked for. The suspicious cases can then be isolated early, and possibly the spread of the disease may be prevented. The patient should be excluded from school until the eruption has disappeared, that is for four or five days. The other susceptible children of the family, may be excluded from school; but such exclusion need only be from 12 to 21 days after the occurrence of the primary case. Disinfection of the room occupied by the patient is unnecessary. The disease is so mild, that it seldom requires any special treatment. A large number of the patients, continue to go about, because the symptoms are so slight that the disease is not recognized.

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CHAPTER CLVII

FILATOW-DUKES' (FOURTH) DISEASE

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The absolute proof of the existence of a so-called Fourth disease, will only be obtained when the specific virus of this condition, is definitely known. However there is already, I believe, sufficient clinical evidence to warrant the consideration of this as a separate entity. It is characteristic of the exanthemata, that they always breed true. The Fourth disease is not common, it is not very communicable; therefore we do not often have an opportunity to study the disease thoroughly. Sporadic cases give us very little help. It is only in institutions, that the problem can be satisfactorily studied. Like other observers, I have seen patients with a scarlatiniform eruption, in whom nearly all the characteristic symptoms of scarlet fever were absent. These eruptions were scarlatiniform from the *beginning*, often disappeared within 24 to 48 hours, and were associated with very little rise of temperature, and very slight constitutional disturbance. Most of these patients were perfectly well within three or four days. As early as 1885 Filatow[1] published his first observations on this disease, which he then termed rubeola scarlatinosa, in contradistinction to rubella, which he called rubeola epidemica. In 1894 and again in 1900, Dukes[2] described this as the Fourth disease. His description was based on three small epidemics which occurred at Rugby school. His conclusions were: (1) Although the Fourth disease resembles scarlet fever in many features, it cannot possess any affinity with that disease, as both diseases occurred concurrently in the same epidemic. (2) Some of the sufferers had both diseases in the same epidemic. (3) One patient had scarlet fever followed by the Fourth disease. (4) Several had the Fourth disease followed by scarlet fever. (5) In one epidemic of Fourth disease nearly one-half the patients had rubella the year before.

The patients reported by Filatow also had an attack of scarlet fever subsequently; and those reported by Weaver[3] were at first thought to have had two attacks of scarlet fever, but one of the attacks was later recognized as having been the Fourth disease.

In 1910 through the kindness of my colleague Dr. Sidney Haas, to whom I am also indebted for the notes of the cases, I had an opportunity of seeing a number of the patients who were infected in an epidemic of the Fourth disease which occurred in an institution in New York City. The total number of children in the institution at that time was 144. They were divided into three groups: Infants under one year; infants between one and two years; and children from two to seven years. The last group occupied a number of wards. In all 16 cases developed. The youngest patient was 11 months of age; there was one between one and two years; two between three and four years; seven between four and five years; three between five and six years; and two between six and seven years. There were six boys and 10 girls affected. In one ward seven cases occurred; and there was not a complete isolation of each ward. The first case occurred on February 24, the next two on March 4, and March 6; that is after an incubation period of 8 and 10 days; the next cases which occurred in the same ward, presented the eruption on March 20; an incubation period of 14 or 16 days; the next on April 1, that is after 12 days; the next, 10 days later on April 11; and the last two cases in that ward occurred on April 23, that is after an incubation period of 12 days. It will be noted that in not a single instance was the period of incubation less than eight days, and in most it was from 10 to 12 days. The course of the disease may be illustrated by two cases, which occurred in the same ward, the first was a moderately severe, the second a mild case. As the first occurred on April 11, and was the only case in the ward, and the second occurred 12 days later, it is highly probable that the one infected the other, and the difference in the clinical course was not due to a difference in the infectious material, but to a difference in the individual reaction.

The first was a female child, four years of age, in whom on the *first day* a *scarlatiniform* eruption was observed on the face, chest and back, but most marked on the wrists, chin, and hands; the temperature (Fig. 69) was 102.2 degrees. The patients also had enlarged tonsils, but these had been present previous to the illness. On the second day the eruption was beginning to fade on the face. There was sneezing, coughing, a slight soreness of the throat, and some enlargement of the lymph-nodes. A fine papular eruption was seen, chiefly on the legs, and the temperature reached its highest point, 103.4 degrees. On the third day, the eruption on the body was disappearing; there was slight desquamation on the face, and a nasal discharge. On the fourth day; some pain in the throat, enlargement of the cervical lymph-nodes. The skin was dry, and there was slight desquamation on the face, chest and back. On the fifth day, a croupy cough, nasal discharge, and slight desquamation. On the sixth day, the rhinitis and laryngitis had improved, and slight desquamation was seen on the abdomen and thigh. The catarrhal symptoms continued so that the temperature did not return to the normal until the fourteenth day. The desquamation was no longer visible at that time.

The second patient was a female child, six years of age. On the first day a scarlatiniform eruption was seen on the face and chest. On the second day the eruption had spread over the body to the groin, and to the proximal portion of the extremities. The tongue retained its normal appearance, the lymph-nodes were slightly enlarged. On the third day, the eruption had disappeared, there was a slight cough, nasal catarrh, enlargement of the tonsils, and cervical nodes. On the fourth day slight desquamation was seen on the nose and ears. There

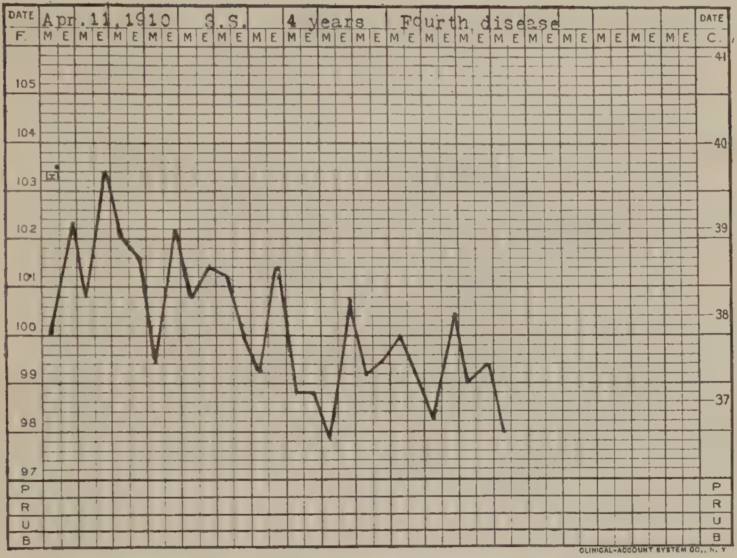

FIG. 69.—Temperature curve in a moderately severe case of the Fourth disease. Patient, four years old.

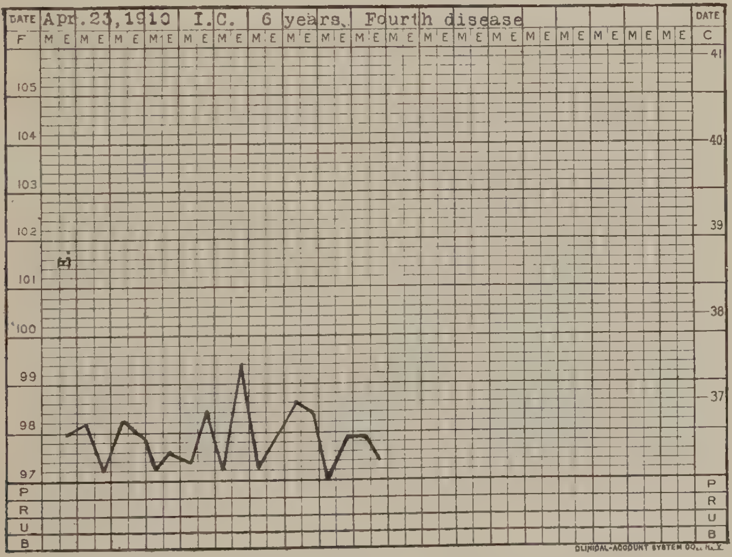

FIG. 70.—Temperature curve in a case of the Fourth disease. Patient, six years old.

was a slight desquamation and enlargement of the lymph-nodes until the eleventh day. In this case the maximum temperature was 99.4 degrees (Fig. 70).

In all of these patients the eruption was scarlatiniform from the *beginning,* there was no initial vomiting, no marked angina, no strawberry tongue, no rapid pulse. The eruption spread very rapidly over the entire body, and disappeared very quickly. Marked constitutional disturbances were absent, and in none was there a complicating otitis, suppurative adenitis or nephritis. The eruption appeared chiefly on the chest, back and groins; in other parts the skin was dry and rough, and was described as being like goose flesh. Desquamation was noted as marked in four cases, absent in two cases, and moderate in the remainder. The maximum temperature was not over 101 degrees in most cases, and in many it was not over 100 degrees

Etiology.—This is entirely unknown. When the specific cause is discovered, the entire question will be cleared up.

Susceptibility.—The disease is much less communicable than measles, probably even less communicable than rubella or scarlet fever. In the small epidemic of which I have given a brief account, only 11 per cent. of the children were infected. This is about one-half the communicability of scarlet fever. In the two epidemics reported by Dukes at Rugby only 16 and 19 boys were infected.

Age Incidence.—All ages, with the possible exception of early infancy are susceptible. The *mode of infection* is not known, but it is probable that the infectious material is conveyed in the nasal and oral secretions; and as the catarrhal symptoms are slight or absent, this may account for the slight communicability of the disease. Infection takes place only when the contact is very intimate. The *period of* incubation appears to be from 9 to 21 days, most frequently from 12 to 15 days.

Symptomatology.—Prodromal symptoms are usually absent, the first manifestation is the eruption. In a few cases pain in the throat, headache, and loss of appetite may be present, but initial vomiting is extremely rare. Catarrhal symptoms are mild or absent.

The **eruption** usually appears first upon the face, chest and back, and spreads very rapidly, in the course of 24 hours over the rest of the body. The individual lesions consist of small bright red punctate spots, closely set together, so that eruption is scarlatiniform in character. In some regions these spots may be bound together by a diffuse erythema. In some cases, a large part of the body may remain free from the eruption. The eruption disappears in 48 hours, without pigmentation of the skin. Desquamation, if it occurs, begins immediately; it is usually moderate, but in some cases may be very well marked. However as against that of scarlet fever, it does not last more than two weeks.

The **temperature** is usually not over 101 degrees, and in many cases not over 100 degrees. Exceptionally a maximum of 103 degrees may be reached. It subsides quickly, within a few days, unless the catarrhal symptoms and glandular swelling are marked, so that the patient is practically well in a week or 10 days. The pulse is not accelerated.

The **tongue** may be slightly coated, but does not afterward present the so-called strawberry appearance so regularly seen in scarlet fever. The **throat** may be reddened, but does not present the marked angina of scarlet fever. The **lymph-nodes** are usually enlarged, sometimes painful, but this is not so constant or so marked as in rubella. This enlargement may persist for some time after the patient has recovered. The glandular enlargement appears early in the disease, and suppuration does not take place as in scarlet fever.

Complications.—The course of the disease is mild. Most patients are well within a few days, so that it is difficult to keep them in bed. Otitis media, pneumonia, adenitis, nephritis do not occur.

Diagnosis.—In sporadic cases, except when other children of the same family are affected, the diagnosis may be impossible. In schools, asylums, and other institutions, where there are large numbers of children, the opportunity for making a definite diagnosis, is much greater. In all doubtful cases, especially at the beginning of an epidemic, the patient should be isolated immediately. However it is a matter of very great importance whether the diagnosis of **scarlet fever,** or of the Fourth disease is made. If scarlet fever, the patient is usually quarantined for five weeks. This entails a certain amount of discomfort and expense. Again if a patient with the Fourth disease is placed in a ward with scarlet fever patients he may contract that disease. If these very mild cases are looked upon as the Fourth disease, they can be isolated carefully for one week, and if at the end of that time, the acute symptoms have disappeared, and the temperature is normal, a longer isolation is unnecessary. The desquamation certainly does not convey the infectious material. As a medical inspector in the Department of Health of the city of New York, I had an opportunity of seeing a number of these cases which were at that time considered as scarlet fever. They were all quarantined for five weeks, and a great deal of unnecessary annoyance resulted.

The differentiation cannot be made with certainty from the appearance of the eruption alone, but in the Fourth disease there is a striking disproportion, between the distinctness and the profuseness of the eruption and the mildness of the constitutional disturbance. The characteristic symptoms of scarlet fever, the incubation period of seven days or less, the initial vomiting, the marked angina, the strawberry tongue, and the continuous high temperature and rapid pulse are absent. The whole course of the disease is milder, and complications rarely if ever occur. These diseases always breed true, so that when scarlet fever, rubella, or the Fourth disease occurs in an institution, each causes only other cases of the same disease. If the patient has had an attack of typical scarlet fever, it is very improbable that he will have a second attack. It is not at all unlikely, that patients who were supposed to have had a mild and a severe attack of scarlet fever, really had one attack of scarlet fever and one of the Fourth disease.

If the term **rubella** is limited to the disease as described in Chapter CLVI, the differentiation ought not to be difficult. As has been pointed out, in rubella the eruption is morbilliform at the *beginning*, and if later in the disease, certain parts present a scarlatiniform character, some areas will be found in which it is distinctly morbilliform. In the Fourth disease the eruption is scarlatiniform from the beginning, and the individual lesions are smaller than in rubella. The history of a previous attack of rubella is helpful. It is said by some authors that in the same epidemic, or at the same season, they have seen patients with rubella who had a morbilliform and others who had a scarlatiniform eruption. This is not proof that they represent two different forms of the same disease. It is not at all improbable that both diseases, rubella and the Fourth disease were prevalent at the same time. In Fig. 71, the seasonal incidence of measles, rubella, and scarlet fever in New York City in 1916 and 1917 is shown. In 1916 there were the average number of cases of measles, and of scarlet fever; but very few cases of rubella. In 1917 there were a somewhat larger number of cases of measles, the average number of cases of scarlet fever; but an epidemic of rubella. A few cases of measles were probably diagnosed as rubella, and a few of rubella, were probably diagnosed as measles; but if there had been cases of rubella

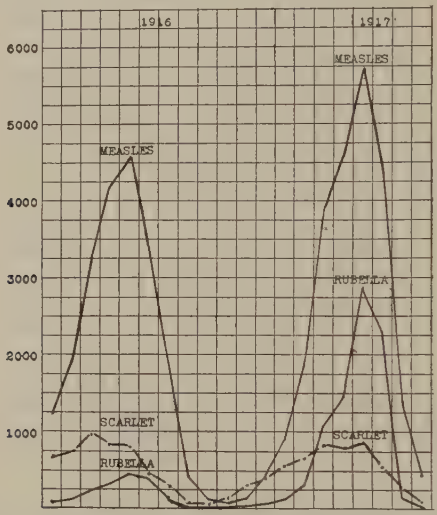

FIG. 71.—The seasonal incidence of measles, rubella, and scarlet fever, New York City, 1916 and 1917.

	1916			1917		
	MEASLES	RUBELLA	SCARLET FEVER	MEASLES	RUBELLA	SCARLET FEVER
Jan	1242	86	680	899	108	578
Feb	1894	113	753	1871	285	657
Mar	3281	225	948	3914	1085	822
Apr	4208	346	842	4634	1468	775
May	4579	475	791	5736	2860	872
June	3393	395	489	4355	2279	515
July	1813	132	300	1368	162	267
Aug	417	29	78	480	33	105
Sept	119	14	72			
Oct	74	11	159			
Nov	127	17	267			
Dec	456	26	435			

with a scarlatiniform eruption, some would undoubtedly have been diagnosed as mild scarlet fever, and the larger number would have given a distinct rise in the curve of scarlet fever. However this form, that is the Fourth disease, was not prevalent, we had simply an epidemic of rubella. As the curve shows measles and rubella may be prevalent at the same season; and I have often seen children who had these two diseases within a few weeks. In one of the epidemics described by Dukes, scarlet fever and the Fourth disease were prevalent at the same time, and several boys, had both diseases.

Treatment.—The disease is usually so mild in character, that little or no treatment is required. The patient should be kept in bed until the acute symptoms and the fever have disappeared.

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CHAPTER CLVIII

EPIDEMIC MENINGITIS

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Definition and Terminology.—Epidemic meningitis may be defined as a slightly contagious, infectious disease caused by the invasion of the meninges by the meningococcus (diplococcus intracellularis meningitidis of Weichselbaum). This disease occurs both sporadically and epidemically and is characterized by local and general symptoms of great irregularity in both number and severity.

A great variety of names has unfortunately been applied to the disease. Epidemic cerebrospinal meningitis is the one most commonly used, but it is needlessly awkward in that the term "cerebrospinal" is unnecessary and even misleading. It seems to imply that in other forms of meningitis the infection is limited to the meninges of either the brain or cord. This is not so except, of course, in the case of a localized meningitis. The term "epidemic" may be objected to in that the disease occurs sporadically as well as epidemically but, so far as is known, the meningococcus is the only organism causing epidemics of meningitis. Hence, this term defines the etiologic factor quite as accurately as does Heiman and Feldstein's[1] "meningococcus meningitis." This designation is an excellent one, however, and is open only to the objection that it has not been generally used; hence, some time would be necessary for physicians to become accustomed to it. "Epidemic meningitis" would probably more quickly replace the term "epidemic cerebrospinal meningitis." Netter and Debrè's[2] "La Méningite Cérébro-spinale" and Foster and Gaskell's[3] "Cerebrospinal Fever" are both open to the objection that they apply equally well to meningitis due to the pneumococcus, streptococcus or other pyogenic organisms. Various other names have been applied—spotted fever, petechial fever, brain fever, black fever, etc., but they have been used only in certain localities. By the Germans the disease is called "Epidemische Genickstarr," a rather inadequate term since it draws attention to a symptom present also in other forms of meningitis.

History.—It is difficult to determine the nature of many diseases resembling meningitis described by early authors. If petechiæ were the most prominent symptom of epidemic meningitis and confined to this disease, the task would be comparatively simple. But the eruption and nervous manifestations are variable and in some cases so closely resemble typhus or the meningeal type of typhoid, for instance, that it is difficult to draw a dividing line. The first distinct record of petechiæ as a symptom was made by Jacobus de Partibus, a French physician, who died in 1465. From that time we have more or less complete accounts of epidemics in which petechiæ are described as occurring. Many of these descriptions do not suggest epidemic meningitis to us, and in other instances the accounts are too meager to judge. Webber[4] gives a most excellent review of the history of early epidemics accompanied by petechiæ, and indeed of the whole subject of epidemic meningitis up to 1866.

The first account leaving no room for question is that of an epidemic in Geneva in 1805 lasting three months. The disease was described most excellently by Vieusseaux[5] as to the clinical manifestations and by Matthey[6] as to the post-mortem findings.

This disease first appeared in epidemic form in the United States in March, 1806, at Medfield, Mass. It was admirably described by Danielson and Mann[7] in a contribution to the Medical and Agricultural Register, "A singular and very fatal disease which lately made its appearance in Medfield, Mass." During the next few years it spread to Connecticut, Vermont, Maine, Virginia, Kentucky, Ohio, New York, Pennsylvania and also to Canada. In this American epidemic, the term "spotted fever" was first used. A description of the disease was written by North[8] in 1811—"Treatise on a malignant epidemic called spotted fever." The most extensive and complete study of the disease from a historical point of view up to 1882 is found in Hirsch's[9] "Treatise on geographical and historical pathology." He groups the epidemic prevalence of the disease into four periods, between which it was comparatively quiescent. The first period is from 1805 to 1815; the second from 1837 to 1850; the third from 1854 to 1875; the fourth from 1876 to 1886. Osler[10] suggests the fifth from 1896 to the present. A study of the distribution of these epidemics shows that they have occurred in practically every civilized country in both the northern and the southern hemispheres from the equator to within the arctic circle.

Epidemiology.—The outbreaks of epidemic meningitis present there features not seen in other epidemic diseases with the exception of poliomyelitis. As a rule, the epidemics do not show a continuous extension. Places widely separated are often simultaneously affected. The proportion of the inhabitants contracting the disease is usually very small, not more than 6 to 8 per 10,000 in larger cities. The occurrence of more than one case in a family is comparatively rare. According to Bolduan and Goodwin,[11] there were only 88 instances of more than one case in a house among 1500 cases in the New York epidemic of 1904 to 1905.

In studying 500 cases of epidemic meningitis since 1910, we have seen more than one case in a house in only 13 instances.

In Case 9, the boy who was sleeping with his two sisters went to bed at the usual hour complaining of a little headache and was found dead in the morning. He had vomited during the previous evening.

Table 1.—Occurrence in the Same Family of Secondary Cases of Epidemic Meningitis

Primary case	Age, years	Secondary case	Age, years	Interval
1. Child	11	Mother	....	3 months
2. Man	....	Brother	....	2 weeks
3. Brother and sister. Taken sick same afternoon.	....	Daughter of sister.	....	5 days
		Man in another apartment. No history of direct contact.		4 days
4. Girl	14	Brother	3½	2 days
5. Girl	9	Sister	5	4 days
6. Boy	4	Sister	2	1 day
7. Girl	....	Sister	....	9 weeks
8. Boy	4	Sister	7	8 days
9. Boy	4	Sister	8	7 days
		Sister	10	12 days
10. Boy	3	Brother	7	19 days
11. Boy	14	Sister	3	3 days
12. Boy	3½	Sister	5	2 days
		Sister	16 mos.	3 days
13. Boy	15	Brother	7	3 days
		Brother	1	17 days

The diagnosis was never absolutely established, but the sudden death and the subsequent development of meningitis in one and probably in both sisters makes this diagnosis most probable. The eight year old sister was convalescing when seen, and the diagnosis was not established by lumbar puncture in her case either although, clinically, it had been a case of epidemic meningitis. In the sister of 10, the diagnosis was confirmed by lumbar puncture. In Case 12, the diagnosis was not confirmed in the two secondary cases. The child of five died within 20 hours of the onset, and a lumbar puncture was not performed. The child of 16 months died within 18 hours, and the spinal fluid, which was withdrawn just before death, was normal. Petechial spots were beginning to appear, however, and a diagnosis of meningococus sepsis was made. It would seem improbable that secondary Cases 1 and 7 were really due to contagion from the primary cases as the time elapsing is much longer than that commonly accepted as the period of incubation. One may ask why these individuals, who were evidently susceptible to the disease, did not develop meningitis when they were so directly exposed. It is possible that these secondary cases had remained carriers since their exposure, and the disease had developed when their resistance for some reason had broken down. On the other hand, they may have been exposed a second time during a period of lowered resistance. Such occurrences are not uncommon in the case of diphtheria, scarlet fever and other infectious diseases. In these 500 cases at least 2000 other members of the families represented were directly exposed to say nothing of numerous neighbors.

These two features, the low morbidity rate and the low degree of contagion, would seem to show that most people have a rather high natural immunity to the disease. This seems to be the case also with poliomyelitis because so few who are directly exposed contract it. The infrequency with which a history of direct exposure can be obtained from a patient would seem to show that most cases are contracted from carriers. This may take place indirectly or by casual contact since the patient usually knows no one who has been at all associated with any other case. Physicians, nurses and others in attendance on the sick are only rarely infected. Reports of contagion in hospitals are very few, and these occur usually during times of epidemics. Outbreaks of the disease in institutions, with the exception of garrisons, are unusual. The disease can often be shown to spread along routes of travel as indicated by its frequent appearance in ports. According to Netter and Debre,[2] it followed the movement of the Eighteenth Regiment of the French Army through France in 1837 to 1850. It has a special tendency to break out among troops due perhaps to the assembling of men from widely separated localities. Some of the men coming from places where meningitis has been present are carriers, while others from uninfected communities are untested as to their immunity. Once started among troops the disease frequently spreads to the civilian population, as in England in 1914 to 1915.

The chief factor in the spread of epidemic meningitis as sporadic and epidemic cases seems to be the carrier, because a history of exposure to a person suffering from the disease can be so rarely obtained. Royster and McDowell[12] brought this out in a report of an outbreak at Norfolk, Va. In a large proportion of the cases there was a history of contact with some one connected wth the Navy Base or Navy Yard, where cases of meningitis had been developing. No connection was found between other cases except in one instance of a mother and child. It must be borne in mind, however, that in certain of the camps no relation obtained between the number of carriers and the number of cases. In a test made at a summer school by Dr. A. W. Williams[13] of the Research Laboratory, about 11 per cent. of carriers were found among 500 students, none of whom had been in contact with cases so far as was known. Furthermore, no cases developed during the summer in spite of the presence of the carriers. In other words, carriers appear to be innocuous under certain conditions. Moreover, it appears to be practically impossible to protect adequately a susceptible person from exposure to either poliomyelitis or epidemic meningitis.

While the presence of the meningococci in the naso-pharynx of patients had been demonstrated earlier by Councilman, Mallory and Wright[14] and by Kiefer,[15] their presence in the naso-pharynx of contacts was first shown by Albrecht and Ghon[16] in 1901. Since then, much

Observer	No. examinations	Positive carriers	Percentage
Goodwin and von Sholly[17]	(*a*) 45 (contacts)	5	11.1
	(*b*) 55 not exposed	0	0.0
Diudonne[18]	(*a*) 68 contacts	5	12.8
	(*b*) 29 remote contacts	4	13.8
	(*c*) 20 not exposed	0	0.0
Osterman[19]	(*a*) 24 close contacts	17	70.8
	(*b*) 51 remote contacts	2	4.0
	(*c*) 10 not exposed	0	0.0
Bochalli[20]	(*a*) 16 close contacts	10	62.5
	(*b*) 114 remote contacts	13	11.4
	(*c*) 355 more remote contacts	19	5.4
	(*d*) 40 not exposed	0	0.0
Bruns and Hohn[21]	(*a*) 3154 in community in which epidemic prevailed	465	14.7
	(*b*) 609 close contacts	224	36.78
von Lingelsheim[22]	(*a*) 387 close contacts	28	7.23
	(*b*) 127 not exposed	0	0.0
	(*c*) 184 children not exposed	0	0.0
Herford[23]	(*a*) 172 close contacts	43	25.0
Trautman[24]	(*a*) 261 close contacts	24	9.2
Mayer, Waldmann,[25] Furst and Gruber.	(*a*) 1911 contacts	47	2.46
	(*b*) 9111 not exposed	158	1.78
Kolle and Wassermann[26]	(*a*) 114 not close contacts	2	1.8
Droba and Kucera[27]	(*a*) 160 not exposed	0	0.0
Kutscher[28]	(*a*) 56 not exposed	4	7.4
Huber and Kutscher[29]	(*a*) 408 not exposed	8	2.0
Bethge	(*a*) 187 contacts	60	32.0
Hachtel and Hayward[30]	(*a*) 97 contacts	15	15.4
Black	(*a*) 801 close contacts	227	28.3
Flack[31]	(*a*) 275 not known to be exposed	6	2.2
	(*b*) 832 possibly exposed	41	4.9
	(*c*) 1629 contacts	139	8.53
Schorer[32]	40,000	3290	3.2
Mathers and Herrold[33]	15,000 (close contacts showed a very high percentage, 26.7)	....	3 to 6 (1.2 chronics)
Bassett-Smith[34]	26,543 (non-contacts)	....	4.7
Glover[35]	12,000 (with reference to overcrowding and season)	....	5 to 41*
Stone and Truit[36]	195,904 (cultures taken at different times. Not this number of men)	4197	2.1
Rossiter and Minaker[37]	8518	261	3.16
T. N. Basset[38]	4730 (non-contacts)	....	1.12
	(Certain number in contact with known carriers)		5.77
Reddin[39]	13 groups of contacts	....	6 to 35
	6 groups of non-contacts	....	1 to 26
	3000 (in another group)	300	10.0

*Due mainly to overcrowding. First three months of year show highest rate.

work has been done along this line, especially during the War. The most important of the earlier studies is shown in the following compilation made from Frost, Public Health Bulletin, 1912, with the addition of more recent work. The work done during the War has been too voluminous to tabulate in full. The data from certain camps only is given.

A study of the preceding figures shows, in general, a low percentage of carriers among those not known to be exposed and a varying percentage among those in close contact. It shows also, in the figures of Bochalli,[20] Flack,[31] Mathers and Herrold,[33] and Glover,[35] that the percentage of carriers increases with the closeness of contact, as might be expected. The percentage of carriers also varies, according to Netter and Debré[2] and others, with the time at which contacts were examined with reference to the beginning of the disease, their social condition (which is obviously quite intricately involved with the question of closeness of contact, the poorer people usually being more closely crowded than those in more comfortable circumstances), the season, and the intensity of the epidemic.

According to Netter and Debré,[2] carriers retain the meningococci usually for less than three weeks after exposure, sometimes, however, for three, four or even seven months. In general, Mayer, Waldman, Furst and Gruber[25] agree with this statement. They classify carriers as temporary, persistent and periodic and found that of 96 carriers, 81.25 per cent. belonged to the first, 12.5 per cent. to the second, and 6.25 per cent. to the third group. Flack[31] studying 185 cases found the average duration to be about four weeks, 5 per cent. lasting over 12 weeks. Rossiter and Minaker[37] found the time of 173 treated carriers to be from three weeks to three months. Reddin,[39] in dealing with 100 carriers, found that under treatment 16 per cent. cleared up in three weeks, 7 per cent. in 40 days, while the remainder were intermittent, that is, gave positive cultures after three successive negatives had been obtained. From these reports the disappearance of the meningococci from carriers corresponds very well with their disappearance from patients, for according to von Lingelsheim,[22] Goodwin and von Sholly[17] and Netter and Debré,[2] the percentage of positive cultures from patients decreases very rapidly after the first week and is very small, 4.3, 6.25 and 25 per cent. respectively, after the third week. It will be noted that Netter and Debré's[2] figures are much higher than those of the other investigators. Embleton and Stevens[40] found the average duration of meningococci in convalescents to be six months; in 49 cases the time was less and in 37 cases it was longer. Netter and Debré[2] state that there are twice as many carriers among the poor as among the well-to-do, 31.35 and 15.38 per cent. respectively.

The influence of the season is shown by results given by Bruns and Hohn,[21] who found in March, 61 cases; in April, 50; in May, 45; in June, 36.6; in July, 27, and in August, 8.5 carriers per hundred contacts. Netter and Debré found an average of 41 carriers per hundred contacts in March, April and May and 26 carriers per hundred contacts in June, July and August. Similar results were determined by the English workers, Glover,[35] for example, who found the maximum number of carriers in January, February and March.

In regard to the relation between the severity of the epidemic and the number of persons becoming carriers, Netter and Debré give the following figures: During a very severe epidemic in Silesia in 1904 to 1905, 32 carriers developed per hundred contacts. In a mild epidemic in Hamburg, in 1907, there were only 9.6 carriers per hundred contacts; while in an epidemic in Paris in 1908 to 1909, more severe than at Hamburg but much less so than that in Silesia, there were 22.7 carriers per hundred contacts. In this connection, it may be mentioned that the number of carriers developing from sporadic cases seem to be few. During the past 13 years in connection with our work in the meningitis division of the Health Department of New York City, we have attempted from time to time to determine the presence of carriers among the families of patients we have treated. While the work done six or seven years ago yielded a small percentage of carriers (the exact figures have been lost) a series of contacts examined during the spring and summer of 1917 showed only a very few carriers. It may be stated that there has been no tendency for cases to recur in the same tenement or neighborhood. We should expect this to occur, if the convalescents or contacts were acting as carriers and actually infecting others, thus constituting a menace.

The treatment of carriers has received considerable attention during the past few years. An extended account of this work is published in the Special Report Series No. 3 of the Medical Research Committee.[41] Spraying and douching with 1 per cent. formalin, 0.1 per cent. potassium permanganate and liquor chlori were tried with so little success that they were soon discontinued. Vapor chambers were devised using chloramin T (after Dakin) or 1.2 per cent. zinc sulphate. The chloramin proved to be rather more efficacious but also more irritating than the zinc sulphate. Dunham and Dakin[42] have devised a spray of chloramin T in oil which is used with a hand spray. This is, of course, much more convenient and more easily available than the vapor chamber. Perhaps none of these methods has been used sufficiently to prove or disprove its value. Of course, the meningococcus carriers tend to clear up spontaneously, especially as warm weather approaches, and it is not easy to determine how much influence the disinfecting vapor or spray may have. There is no record of argyrol being used in these tests. Argyrol, as tested at the Research Laboratory by workers in the meningitis division, is highly antiseptic for the meningococcus. It can be freely used in the nose and throat. It is remarkable for its power of diffusing through the mucus and for its persistence in the nasopharynx. For these reasons, we have repeatedly recommended it for contacts, but unfortunately, we have not had the opportunity to test it on carriers.

In connection with the subject of carriers, it should be borne in mind that the "periodic" or "intermittent" carrier offers a difficult problem, because he may be shown to be a carrier and a source of infection again, even after three negative cultures have been obtained. An example of this has recently come to our attention. A soldier who had been a carrier, but who had been discharged after three negative cultures, returned home some months later. His baby promptly developed meningitis, and it was found that the father was again a carrier. After treatment he became negative a second time.

Chronic carriers are often found to have some abnormality of the nose or throat, diseased tonsils, adenoids, infected sinuses or obstructions. Cleminson[43] worked up this phase of the subject quite thoroughly and obtained successful results in clearing up carriers after the abnormality had been corrected.

It has been generally observed that very few carriers develop meningitis.

The technic for detecting carriers is as follows: The upper part of the posterior wall of the pharynx is swabbed, and plates of suitable media are immediately inoculated. The swab used may be an ordinary swab on a wire bent at a convenient angle to reach the upper posterior wall of the pharynx or a covered swab devised by West. In this, the wire and swab are enclosed in a narrow glass tubing bent at the end. After the tube is inserted into the throat, the swab is pushed out of the tube, the culture taken, and then the swab is pulled back into the tube. The object is to avoid contamination, but the procedure produces more discomfort and gagging and consumes more time than does the taking of a culture with an ordinary bent swab. For these reasons, Foster and Gaskell[3] and many of the army workers have discarded it. The identification of the meningococcus will be discussed under the section on bacteriology.

While it has been long accepted that the meningococci enter the body by way of the nasopharynx, the path thence to the meninges has been extensively discussed. Some believe that the meningococci pass to the base of the brain by direct extension through the sphenoidal sinuses, the ethmoid bone, or through the Eustachian tube, the middle and internal ear. There is little proof of this. Others believe the spinal cord is infected by the passage of the meningococci along the lymphatics of the spinal nerve roots. This view has not been adequately supported. Most workers believe that the meninges are ordinarily infected secondarily from an invasion of the blood, this invasion being usually transient, a bacteremia rather than a septicemia. This last view is supported by the fact that a varying percentage of positive bood cultures is obtained early in the disease. The percentage varies with the stage of the disease and the type of infection, being very high in the septicemic type. Furthermore, the early symptoms of meningitis indicate an acute general infection. The results obtained by cultures will be more fully discussed under the subject of blood culture. Although it is proved that in many instances the meningococci reach the meninges by way of the blood stream, it does not follow that this is the exclusive path.

Season.—Epidemics have usually made their appearance and reached their maximum in the winter and spring. In a few instances, given by Hirsch,[9] they have begun in the summer. In the New York epidemic in 1904 to 1905, the maximum was reached in May and March, respectively. The sporadic cases show the same disposition to increase in the late winter and spring. We have seen the seasonal occurrence of cases as follows: July to October, 64; October to January, 87; January to April, 158; April to July, 209. In view of the wide distribution of the disease and the fact that some few epidemics have occurred in the summer, the temperature, in itself, cannot be the sole determining feature. There can be little doubt that it has some influence, considering the preponderance of cases and epidemics occurring in the winter and spring. Perhaps the variability of the weather at these times has some influence.

Age, Sex, Race.—While cases of epidemic meningitis are seen in all ages, the great majority are in children and adolescents. Exceptions to this occur in epidemics in armies where, of course, there are only adults, in the Italian epidemics in the 'forties, and in an epidemic at Montgomery, Ala. In the New York City epidemic of 1905 to 1906, over 65 per cent. of the cases were in children under 10 years of age, and in the Prussian epidemic at about the same time, 80 per cent. of the cases were below 16 years. The sporadic cases in New York City that we have been studying for the past 13 years show this same high degree of incidence in children. Table 2 shows the distribution of over 1500 cases of meningitis according to age and etiology. It will be seen by a study of this table that a far larger number of cases of epidemic meningitis occurred in the first year of life than in any other one year.

TABLE 2.—DISTRIBUTION OF MENINGITIS ACCORDING TO AGE AND ETIOLOGY

Age	Tubercle bacillus	Meningococcus	Pneumococcus	Streptococcus	Influenza bacillus	Staphylococcus	Colon bacillus	Total
3 months	5	24	3	10	2	0	3	47
3 to 6 months	21	57	4	6	8	0	0	96
6 to 12 months	78	68	11	3	14	2	0	176
Total No. cases under one year	104	149	18	19	24	2	3	319
1 to 2 years	178	79	7	9	14	2	1	290
2 to 3 years	80	36	9	6	6	1	0	138
3 to 5 years	99	80	6	11	1	2	0	199
5 to 10 years	96	104	16	20	3	0	1	240
10 to 20 years	57	101	7	5	3	2	0	175
Over 20 years	48	74	22	12	0	2	0	158
Totals	662	623	85	82	51	11	5	1519

About 50 per cent. more males than females were attacked by the disease in a series of over 500 sporadic cases in New York City. This also is true of poliomyelitis and epidemic encephalitis. Race seems of little importance, considering the wide distribution of the epidemics. In certain epidemics in New Orleans and Memphis, negroes were affected more than the whites, while in Texas, in 1912, the reverse was true.

Periodicity.—As is seen from a study by Hirsch,[9] the epidemics appear in cycles, widespread epidemics or pandemics alternating with periods of quiescence. With the disease once established in a community, there seems to be a periodicity in the increase of cases, at least such has been the experience in New York City where an increase has occurred about every 9 to 12 years. This may be accounted for perhaps by the appearance of a new generation of children, a part of whom are susceptible.

As we now look at it, we would say that the beginning of an epidemic is due probably to the introduction of new strains into a more susceptible population. However, there is much relating to the subject that we do not understand.

Bacteriology.—The specific cause of epidemic meningitis was first discovered by Weichselbaum[44] in 1887 and he called the organism the Diplococcus intracellularis meningitidis. He isolated it from the spinal fluid in six cases of meningitis. This observation was confirmed by other workers, and in 1895 Jaeger[45] isolated from patients in a small epidemic of 14 cases an organism which he believed identical with the diplococcus of Weichselbaum but which differed from it in certain minor details. This led to more or less controversy over the etiology of epidemic meningitis, which was cleared up in part by the work of Councilman, Mallory and Wright[14] and conclusively by Elser and Huntoon.[46]

The meningococcus is Gram-negative and usually occurs in pairs, although other arrangements such as groups and short chains are seen. It takes other stains readily, but these should not be used, especially in smears from spinal fluids, as serious error may thereby arise because the morphology is not sufficiently distinctive to make the diagnosis. In smears from spinal fluids, the organism may be either intra-cellular or extra-cellular. Cultures of the meningococcus show an irregularity of staining that is quite characteristic. This irregularity increases with the age of the culture, but is noticeable in 24 hour growths. It is probably due to the rapid autolysis of the meningococcus. To this autolysis also is due the fact that cultures from material over 12 to 18 hours old are usually unsuccessful.

The meningococcus is aërobic and grows fairly readily on suitable media. In the early generations it will very rarely, if at all, grow on ordinary agar. We have been successful with glucose (2 per cent.), veal agar, pH 7.8 containing one-third ascitic fluid. At present, instead of using ascitic fluid, we add 5 per cent. horse blood (citrated) to the glucose veal agar while it is very hot (about 90°C.). This makes the so-called "chocolate agar." The reaction of the base, that is, pH 7.8, is very important. The organism grows best at slightly under 37°C., about 35 to 36 degrees, and most strains are readily killed if the temperature is inadvertently allowed to rise to around 40°C. When a strain is first isolated, subcultures should be made every day. Later, transplants must be made three times a week if one wishes to keep the largest possible percentage of strains. Even then strains will occasionally die out. Large amounts of the material should be carried over in subculturing. Sometimes, if a strain does not grow well, culturing for a few generations on media containing blood seems to act as a tonic. Some workers prefer sheep-serum agar; Gordon[47] recommends a "pea extract trypsin agar." When ascitic fluid is not available, the ether-rabbit-blood recommended by Gordon[47] may be tried. The blood is obtained by bleeding a rabbit from the carotid, under aseptic precautions, directly into 50 c.c. of 5 per cent. citrate in physiologic salt solution, to give a content of 5 per cent. of rabbit blood. Ether, 10 per cent., is then added, and the whole shaken and allowed to sediment for 24 hours. The clear solution (hemolyzed blood) is then drawn off and bottled—a slight excess of ether being added to each bottle. Four cubic centimeters of this blood is added to each bottle of agar after it is melted and cooled to 50°C.

After having been isolated for some time, the meningococcus will grow moderately well for several generations on veal agar pH 7.8 with or without 2 per cent. glucose. North's semi-solid media is excellent for stock cultures. Löffler's serum is also a fairly suitable medium. Some strains show a tendency to produce a yellowish or brownish coloration, especially in the older cultures. Cultures of the meningococci on glucose ascitic agar show a faint clouding of the media immediately beneath the surface due to the fermentation of the glucose.

Perhaps the most satisfactory medium for the detection of carriers is the vitamin agar, a modification by Williams[13] of the hormone agar, devised by Huntoon.[46] The modifications consist in the addition of 1 c.c. of whole, citrated horse blood to 40 c.c. of agar and in a change of certain details of making. The plates should be poured immediately before they are used. On this media very large colonies of meningococcus develop in as short a time as 14 hours. At the Research Laboratory of the New York Health Department, the following method was used in the detection of carriers. The culture from the naso-pharynx, taken by the West tube, is planted on a plate of vitamin agar near the circumference and thoroughly spread by making 50 or more radiating lines with a platinum loop. At the end of 14 to 18 hours characteristic colonies are fished and tested by slide agglutination against normal serum and antimeningitis serum of high titer, each in a 1:10 dilution. A Gram stain is then done on the test slides. It has been found that the micrococcus catarrhalis and other Gram-negative cocci in the naso-pharynx are ruled out by the agglutination tests; while a Gram-positive coccus and two Gram-negative bacilli which occur in the naso-pharynx and give a definite agglutination, are ruled out by a study of the stained slides. By this method a report may be given in 18 hours. Other methods, too numerous to be described, were employed in the Army and Navy both here and in Europe.

The fermentation reactions are very constant and, therefore, of great importance in the differentiation of the meningococcus from other Gram-negative organisms, especially those found in the nose and throat. Table 3 is taken from Elser and Huntoon.[46]

TABLE 3.—FERMENTATION REACTIONS IN MENINGOCOCCUS DIFFERENTIATION

Organism	Number of strains	Dextrose	Maltose	Levulose	Saccharose	Lactose	Galactose	Dextrin	Mannite	Dulcite	Inulin
Meningococcus	200	+	+	0	0	0	0	0	0	0	0
Pseudomeningococcus	6	+	+	0	0	0	0	0	0	0	0
Gonococcus	15	+	0	0	0	0	0	0	0	0	0
Micrococcus Cat	64	0	0	0	0	0	0	0	0	0	0
Mic. Pharyngis siccus	2	+	+	+	+	0	0	0	0	0	0
Chromogenic Group I	28	+	+	+	+	0	0	0	0	0	0
Chromogenic Group II	11	+	+	+	0	0	0	0	0	0	0
Chromogenic Group III	9	+	+	0	0	0	0	0	0	0	0
Jaeger Mening. (Kiel)	1	+	+	+	+	+	+	0	0	0	0
Diplococcus crassus (Kiel)	1	+	+	+	+	+	+	0	0	0	0

Viability of the Meningococcus.—The meningococcus is rather difficult to cultivate. It is not especially sensitive to sunlight. Elser and Huntoon have found that some strains survive an exposure of eight or nine hours. Drying kills it readily according to most observers, but Elser and Huntoon report that some strains survived 24 hours of desiccation.

TABLE 4.—EFFECT OF DISINFECTANT SOLUTIONS ON MENINGOCOCCI

Solution	Per cent.	Kills in minutes
Hydrogen peroxid	3	1
Corros. subl	0.1 to 1	
Silver nitrate	1	
Carbolic acid	1 to 2	
Lysol	1	
Menthol	9	
Sulphuric acid	1	2
Protargol	2	
Alcohol	70	
Hydrogen peroxid	1	9
Protargol	0.5	

Von Lingelsheim[22] found that emulsions were killed by exposure to 50°C. for one hour, 60°C. for 10 minutes, 70°C. for five minutes, 80°C. for two minutes.

Table 4, showing the effect of disinfectant solutions on the meningococcus, based on Flügge's experiments, is taken from Heiman and Feldstein.[1]

Experiments by members of the meningitis division showed that the meningococcus was very susceptible, in vitro, to the action of argyrol in solutions of from 15 to 25 per cent.

Pathogenicity.—Intraperitoneal injections of live cultures of the meningococcus in guinea pigs cause death in from one to five or six days depending on the size of the dose. Small doses do not produce death, and it is difficult to arrive at a minimal lethal dose on account of the varying resistance of different animals. The culture can usually be recovered from the heart's blood in those dying within the first two days. Guinea pigs are also killed equally readily by the intraperitoneal injections of the autolysate. It is probable, therefore, that death is due to a toxin rather than to the infection. Mice, in the hands of most workers, have behaved with similar irregularity. Hitchens, however, reports fairly uniform results. Rabbits stand the intravenous injection of live cultures of most strains very well, although some strains seem much more toxic than others, producing rapid emaciation and early death, so that it is difficult to immunize with them. Councilman, Mallory and Wright[14] succeeded in producing meningitis in a goat by intra-dural injections. Monkeys develop meningitis after intra-dural inoculations. This has been done by von Lingelsheim and Leuchs,[48] Flexner,[49] Stuart McDonald[50] and others.

Grouping of Strains.—In 1909, Dopter[51] called attention to certain cases of meningitis that failed to respond to the ordinary anti-meningitis serum but cleared up with a homologous serum prepared by him. He found these strains to be culturally like the meningococcus but with different serologic reactions, and he applied to these strains the term "parameningococcus." In 1911, the members of the meningitis division[52] started to investigate the possible grouping of the meningococcus strains, having in mind Torrey's[53] success in demonstrating the grouping of the strains of the gonococcus. The method selected was complement fixation. Of 29 strains tested 14 fell into one group, and eight into another. Three seemed related to the first group but acted so irregularly that they were grouped by themselves. Four were placed for convenience, as in grouping the pneumococcus, in a miscellaneous group, two of which showed no relationship with any other strains and two reacted only with each other. Two of Dopter's[51] parameningococcus strains were tested at this time, one of which reacted only with its homologous serum, as did two of our fourth group; the other reacted with Group II. From this, we concluded that it was perhaps better to consider the different meningococcus strains as falling into various coördinate groups rather than differentiating certain of these by the prefix "para." Wollstein,[54] in a very careful study of the parameningococcus, concludes: "Because of the variations and irregularities of serum reactions existing among otherwise normal strains of meningococci, it does not seem either possible or desirable to separate the parameningococci into a strictly definite class. It appears desirable to consider them as constituting a special strain among meningococci, not, however, wholly consistent in itself."

Gordon[47] divided 32 strains of meningococci into four types by the agglutination and absorption tests. Other strains examined later by him fell into one of these four types. A large percentage of the strains examined by him, 80 per cent. in one series and 85 per cent. in another, fell into his Types I and II. Tulloch[55] and other English workers, in 1917, confirmed the division of all strains into four types. However, in further studies Tulloch began to find subgrouping in Type II and also certain strains that failed to conform to any of the four types. Griffith,[56] working with the civilian population in England, found two fairly well-defined groups and some intermediate strains, in general, Group I, including Gordon I and III; Group II, including Gordon II and IV. Scott,[57] also working in the civilian population, made two groups which he further subdivided and states that a number of strains could not be classified. In France, Nicolle[58] and co-workers studied 200 strains and found two main groups, *A* and *B*, a small group of seven strains *C*, and one strain which they called *D*. In general *A* was equivalent to Gordon I and III, and *B* to Gordon II and IV.

A study of the grouping of the strains found in the sporadic cases of epidemic meningitis seen in New York City was made at the Research Laboratory of the New York City Health Department by Miss Georgia Cooper. Her observations indicated that the four Gordon types are not so homogeneous and inclusive as reported by Gordon. Of 75 spinal fluid strains taken from Department of Health cases, 24 corresponded closely to Type I, four to Type II, and five to Type III. Of the remaining strains, some were apparently not closely related to the Gordon types but were different in their absorptive capacity. A number of strains showed no relationship with any of the Gordon types.

Butterfield,[59] considering the broader relationship, found that his strains, with the exeption of three inagglutinable strains, fell in with the Gordon types or were closely related to them.

Evans,[60] working with the tropin reaction, divided 63 strains into four groups, *R*, *S*, *T* and *U*, and added a fifth group *Z*, containing a small number of irregularly reacting strains. Group *R* was found to be made up chiefly of Gordon Types I and III, Group *S* corresponded to Gordon Type II, Group *T* included various types, and Group *U* was represented by only one strain in this series.

The great importance of the grouping of strains is obvious when one considers the preparation of serum. It is necessary that the strains utilized shall have such antigenic properties that the serum will possess a range of action against as many types as possible and yet, in view of the large number of strains which may be collected, that the keeping of unnecessary strains be avoided.

As we have seen, various serologic reactions have been applied to the study of the meningococcus.

Mention may also be made of the precipitin reaction—most studied by Vincent and Billot.[61] It was suggested by them as an aid in the diagnosis of meningitis. Centrifuged spinal fluid (from an untreated patient) is mixed with immune serum and incubated at 50°C. for from 8 to 12 hours. A clouding of the mixture is a positive reaction. This method has not gained much favor, and in the hands of many workers has given unreliable results.

The study of the opsonic power of serum has been used to a considerable extent in the past for standardizing anti-meningitis serum and to a small extent for diagnosis with human serum. The readings are too indefinite to make it of value in diagnosis, and this difficulty in making readings has led to its being largely replaced by complement fixation and agglutination for standardizing serum. More recently Evans[60] has restudied the method of determining the content of immune opsonins or tropins and has been able by improvements in the method to obtain more accurate results.

The agglutination test is perhaps the most commonly used of any serologic reaction for purposes of identifying the meningococcus, for example, as in studying carriers. As has been stated, combined with absorption it is used by Gordon,[47] Dopter,[51] Tulloch,[55] Nicolle[58] and others, for grouping the strain of the meningococcus. It is also used in testing antimeningitis serum to some extent, especially to see if a serum contains agglutinins and therefore, presumably, other antibodies against particular strain.

Complement fixation has been used to some extent for diagnosis, also for grouping the strains and to a greater extent for the standardization of serum. It has the advantage of giving clear-cut and definite readings.

Antimeningitis Serum.—The following account of the history and development of antimeningitis serum is taken from Park and Williams[13] "Pathogenic Microörganisms." "It is difficult to apportion the credit for the production of the first protective serum. Banhoff and Leprière produced a serum in animals which showed definite protection. The world-wide epidemic beginning in 1904 stimulated a number of laboratories to produce sera in horses with the idea of treating cases in human beings.

"Thus Kolle and Wassermann, Jochmann, Flexner and ourselves immunized horses. . . . In 1905, there was inaugurated, in Hartford, the use of subcutaneous injections of diphtheria antitoxic serum in meningitis. This influenced us to prepare and try the subcutaneous injections of an anti-meningococcus serum. The results reported by physicians in some 20 cases did not seem to establish the fact that any beneficial effects were obtained, so that no further serum was issued. Later, Kolle and Wassermann reported somewhat favorable results in a number of cases from the subcutaneous injection of a serum prepared by them. Meanwhile, a serum prepared by Jochmann was employed by the intraspinal method in a series of cases. This method soon supplanted the subcutaneous injections.

"The first successful use of an immune serum in cases of human cerebrospinal meningitis by the intraspinal method should, therefore, so far as we know, be credited to Jochmann and the physicians who used his serum in the winter of 1905 and 1906. He reported a series of cases treated by the intraspinal method before the Congress for Internal Medicine held in Munich in April, 1906, and published his paper May 17, 1906. He reported 40 cases, but gave details concerning only 17 patients, all treated by Kromer. Five of these patients died and 12 recovered, a mortality of 29 per cent. He directed that after lumbar puncture 20 to 50 c.c. of fluid should be removed and then 20 c.c. of immune serum injected. These injections were to be repeated once or twice if the fever did not abate or returned. He noticed in general a bettering of the headache, stiffness of neck and mental condition. Jochmann showed that in animals colored fluid injected into the spinal canal in the lumbar region passed the full length of the canal. The serum was shown to possess both bactericidal and opsonic power.

"Although the serum prepared in different laboratories in Europe was regularly used after Jochmann's report, it did not receive much attention in this country until Flexner, through his important experiments demonstrating the value of the intra-spinal injections of the serum in infected monkeys, aroused medical interest and paved the way to try out the serum on a large scale. All cases treated by him were subjected to most careful bacterial tests and clinical observation. Eighteen months later, Flexner and Jobling published their report which fully corroborated the earlier results of Jochmann. The serum prepared at the Rockefeller Institute for Medical Research has been sent to many places, both in this country and in Europe. The results obtained have been of the utmost value in arriving at the value of the intraspinal treatment."

At present, the serum is prepared at the Research Laboratory by intravenous injections of live cultures. The dose, at first, is one-twentieth of a slant. This is increased to 8 to 12 slants depending on the reaction of the horse as to temperature and general condition. The interval of injection may be three successive days with a week's rest, according to Amoss and Wollstein,[54] or every fourth day. It has been the custom to utilize for horse immunization a large number of strains. During the past few years, as a result of the more intensive study of the immunological relationship, there has been a gradual reduction in the number of strains employed. The Hygienic Laboratory at Washington recommends the use of selected strains the injection of which will produce antibodies for the majority of strains encountered in this country. About 15 strains are used at present in immunizing the horses. They have been selected from a much larger number, so that they represent the prevailing varieties as based on agglutination, complete fixation and tropin content test on the meningococci isolated from a large number of cases. Ordinarily it takes about five to six weeks for a horse to reach the required titer and during the following month or two the titer of the serum of most horses rises to a higher level and may be maintained there. From 6 to 10 liters of blood can be drawn from a horse every two weeks. At the Bureau of Laboratories it is the practice not to start bleeding a horse until it has been under intensive treatment for at least two months. This may not be necessary but it is done as an extra precaution.

For testing the serum, agglutination, and the complement fixation reaction are utilized by the Health Department Laboratories of the City of New York. To be acceptable, the agglutinin content must be comparable to that of the serum supplied as a standard by the Hygienic Laboratory at Washington. The serum is tested against four representative types, three being Gordon's Types I, II and III and the fourth a strain selected by the Hygienic Laboratory. With the complement fixation reaction, the serum must give complete fixation in 0.001 c.c. The tropin content is tested at Washington. Although there are differences of opinion as to the significance of the different antibody titrations, the feeling is that, lacking a direct and unquestioned means of measuring the therapeutic potency, the selection of serum having a high potency in regard to most of the antibodies will give a serum which will be potent therapeutically. This expresses, in a general way, the conclusions of the Committee on Anti-meningitis Serum appointed by the American Public Health Association.

In connection with this antibody titration, it should be noted that there is an increase in the phagocytosis in the spinal fluid in cases under successful treatment. This indicates that the opsonic or tropin power of the serum may have an important, if not the most important, bearing on its therapeutic value. A protection test similar to that used for the pneumococcus would be the method of choice if the meningococcus were more uniformly infectious and invasive for test animals.

The serum is preserved with 0.2 per cent. trikresol. For a while chloroform was tried instead, on account of objections raised by some physicians, especially Kramer[62] of Cincinnati, who claimed that the trikresol, through some toxic action, was the cause of sudden death in certain cases, especially in young children. No very convincing evidence of this was ever brought forward, and animal experimentation and clinical observation by other physicians seemed to controvert successfully this opinion. Moreover, the chloroform in the serum caused severe pain on injection, as much so that it interfered with the usefulness of the serum both on account of objection to its use by the patient and family, and the interference with regulating the dose due to the struggling and crying out of the patient. A study of the comparison of the two preservatives was published by Neal and Abramson.[63]

The distribution of the meningococcus in the body is of some interest. It may be summarized as follows: The organism may be found in the naso-pharynx both in healthy individuals and in those suffering from the disease. In patients, it is found in the spinal fluid and in the tissues of the central nervous system; and at certain stages, in the blood. It may also be found in the lungs in patients with meningococcic pneumonia; in pus of joints in arthritis; in orchitis, endocarditis, otitis media, cystitis, pyelitis, pleurisy, empyema and other extra-meningeal involvements; and in the lesions of the skin, both hemorrhagic and herpetic.

Pathology.—Since most of our patients were treated in their homes, it has not been possible for us to secure many necropsies. This account of the pathologic findings, therefore, is largely compiled from the following sources: Councilman, Mallory and Wright,[14] Netter and Debré,[2] Heiman and Feldstein,[1] and Foster and Gaskell.[3]

In the first well-authenticated epidemic, that occurring in Geneva in 1805, a post-mortem examination on one case was described by Matthey.[6] In the Medfield epidemic in 1806, five post-mortem examinations were made by Danielson and Mann.[7] Eight necropsies were reported by the Massachusetts Medical Society in 1809.[64] In these reports, attention was called to the difference in the lesions between cases of from 12 to 24 hours duration in which there was only intense hyperemia of the meninges, and cases of longer duration in which there was a purulent exudation. In the French epidemic from 1840 to 1845, changes in the substance of the brain and cord were studied. Strumfell,[65] in 1889, published an excellent description of both the gross and microscopic lesions of the meninges and the brain and cord substance. He brought forward the idea that brain abscesses may arise in the course of a meningitis or may be the result of an unrecognized meningitis, and cited the history in three cases of brain abscess apparently idiopathic that had been preceded by meningitis. It may be noted in this connection that one of our cases became chronic with spasticity after the spinal fluid had apparently cleared up. A large brain abscess associated with hemorrhage was found post-mortem in the motor area. Smears from the abscess were negative.

The lesions, both macroscopic and microscopic, vary greatly according to the stage of the disease.

Macroscopic Lesions.—Cases in which the patient succumbs to an overwhelming infection within 24 hours show mainly an intense hyperemia of the meninges and brain with little, if any, pus formation. There may be hemorrhage in the brain and cord substance. In the acute cases, the patients dying within five or six days, the meninges show in addition to the hyperemia a varying amount of sero-purulent, purulent and, to a less degree, fibrino-purulent exudate. According to Councilman, Mallory and Wright,[14] the meninges of the entire brain are rarely equally affected, the process being much more pronounced in certain locations than in others, especially on the lateral surfaces of the convexity, the parietal and occipital lobes. The meninges covering the cerebellum are always involved, especially on the upper surface. At the base of the brain, there is exudation often distinctly purulent. According to Foster and Gaskell,[3] the localization of the infection depends on the stage of the disease, being most pronounced on the vertex in the more acute types and confined mainly to the base, as a subsequent development, in the milder and more chronic cases. In the more acute cases, the amount of fibrin is small. In the less acute cases, lasting from 5 to 12 days, the exudation is greater and has a tougher, more gelatinous character due to the greater amount of fibrin. The hyperemia is less marked. In the chronic cases of from 15 to 30 days duration, the characteristic changes in the meninges are edema and marked thickening especially at the base of the brain where there may be bands of organized tissue. Councilman, Mallory and Wright[14] cite one case in which masses of partly organized fibrin were found adherent to the walls of the ventricles, and another in which the entire medulla was firmly imbedded in a dense mass of connective tissue. There is little exudation.

The changes in the meninges of the cord are similar to those of the brain. The exudation is most marked along the posterior surface of the cord, usually in the dorsal and lumbar regions.

The lesions of the brain and cord substance are revealed chiefly by microscopic examination. The dilatation of the ventricles is less in the more acute stages and greater in the more chronic conditions. The brain substance is often somewhat softer, and there is injection of the vessels, sometimes even hemorrhage. The substance of the cord is softer, and there is increased injection.

The cranial nerves are somewhat affected, the second, fifth, seventh and eighth being most involved. They are imbedded in exudate and are swollen and reddened. The Gasserian ganglia and olfactory bulbs are swollen and softened. The spinal nerves are imbedded in exudate, and the spinal ganglia are red and swollen. There is often marked exudation around the nerves of the cauda equina.

Microscopic Lesions.—The microscopic lesions, as well as the macroscopic, vary according to the stage of the disease. Purulent infiltration in the meninges with little fibrin is seen in the very acute cases, in which but little change is noted macroscopically. This purulent infiltration increases in the cases of somewhat longer duration. The leukocytes are of the polymorphonuclear variety, stain sharply, and show an almost complete absence of eosinophils. In rare instances, red corpuscles are found in the exudation. There is more fibrin, and it has sometimes undergone hyalin change. In the exudation of this stage, a type of cell is found first described and extensively studied by Councilman, Mallory and Wright.[14] It is from two to eight times the diameter of a leukocyte, has a large vesicular nucleus and faintly staining, granular protoplasm. It takes up other cells especially polymorphonuclear leukocytes. Councilman, Mallory and Wright were able to trace its formation from the cells of the connective tissue and from the cells lining the lymph spaces.

In the chronic cases, the amount of exudation is small and consists of degenerated leukocytes and nuclear detritus. There are very few large cells, and in their place are lymphoid and plasma cells. The substance of the meninges is greatly thickened, the tissue being cicatricial in character and containing few cells. The change in the meninges of the cord are of the same character but not so marked as those of the brain.

Tissues of the Brain and Cord.—According to Councilman, Mallory and Wright,[14] microscopic changes in the brain and cord substance are found in most cases of epidemic meningitis, and they are more marked in this type than in any other purulent meningitis. There is infiltration of the tissue with pus cells, extending downward from infiltrated areas of the meninges, and surrounding the blood vessels which are injected. The cortex is somewhat wider as though edematous. Hemorrhages are occasionally found in the cortex of the cerebrum or cerebellum, also in the white matter. The ventricles are usually altered. There may be destruction of the ependymal lining, and the tissue beneath is edematous. In chronic cases, the surface of the ventricle is often covered with granulations.

The neuroglia shows proliferative changes, especially around areas of hemorrhage or infiltration in the white matter. It is also shown in the cortex, in the tissue of the ventricle, in the cerebellum and in the optic and olfactory nerves. Some changes—alteration in the cell granules and irregularity and atrophy of the cell body—are found in the ganglion cells, especially in the more chronic cases. The nerve fibers show degeneration, especially near the internal capsule.

In general, the same changes are found in the cord as in the brain, but usually they are less marked. The degenerative changes, however, are more marked in the cord than in the brain, particularly in the posterior column.

Diplococci may be found both in the meninges and in the brain, particularly in the acute cases.

Nerves and Ganglia.—The second, fifth and eighth cranial nerves show the most marked changes, an infiltration with pus cells, and in the more chronic cases with epithelioid and plasma cells as well. The fifth nerve sometimes shows an intense neuritis. The seventh nerve also frequently shows considerable infiltration, as do also the third and sixth though to a less degree. The spinal nerve roots show infiltration and degeneration, especially in those sections of the cord that are most involved.

The Gasserian ganglia and the spinal ganglia show purulent ininfiltration occasionally with some hemorrhage and degenerative changes. The condition is probably due to direct extension along the nerves. Diplococci are sometimes found in the sections of the Gasserian ganglia.

Lesions Involving Sight and Hearing.—On account of the frequency and seriousness of involvement of the eye and ear in epidemic meningitis, the pathologic changes which may take place in the visual and auditory apparatus deserve special consideration. A very complete description of the eye complications and their pathology is found in Netter and Debré,[2] and in Councilman, Mallory and Wright.[14] According to Netter and Debré, the lesions may be divided into two classes: First, the inflammatory and suppurative lesions, as conjunctivitis, iritis, keratitis, iridochoroiditis and metastatic ophthalmitis. They think these infections reach the eye directly from the rhinopharynx or by way of the blood. The second class of lesions includes the involvement of the nerves by extension of the inflammation from the meninges, the ocular paralyses, changes in the pupils not arising from an iritis, and various disturbances of vision.

Councilman, Mallory and Wright[14] divide the eye lesions into three classes: First, a neuritis or degeneration of the nerves of the eye, especially the oculo-motor, due to their involvement in the exudation at the base of the brain without any extension of the process along the nerves to the orbit or eye. This gives rise to the various paralyses of the eye muscles. Secondly, the inflammation of the meninges may extend directly from the brain into the eye usually along the pia-arachnoid of the optic nerve. Studies of sections of this nerve throughout its entire length have convinced these investigators that this is the mode of entrance of the infection. Due to this cause are the cases of irido-choroiditis and, in some instances, lesions of the cornea. Thirdly, those lesions due to loss of sensation arising from neuritis of the fifth nerve and destruction of the Gasserian ganglion.

The ear complications are also discussed very fully by these authors. The auditory nerve usually shows, according to Councilman, Mallory and Wright, exudative and degenerative changes due to the extension of the inflammatory process from the meninges. This process may extend and involve the labyrinth and even the cochlea and the organ of Corti. The fibrino-purulent exudate is soon organized into an osteoid connective tissue. Those rare cases of deafness that clear up are probably due to a serous infiltration of the labyrinth and nerve, which readily subsides. Otitis media is comparatively rare in epidemic meningitis. Many authors believe that cases of sudden deafness may be due to mild and unrecognized attacks of epidemic meningitis.

Other Organs.—According to Councilman, Mallory and Wright, the spleen, liver, kidneys and heart show only the lesions of an acute infection. According to Maclagan and Cooke,[66] a hemorrhagic adrenalitis occurs in the fulminating type of epidemic meningitis. A meningococcic endocarditis has been described in cases, however, in which there was no evidence of meningitis. Adami and Nicholls[67] give purulent pericarditis as a complication.

Councilman, Mallory and Wright found in their necropsies eight cases of pneumonia due to the meningococcus. The character of the inflammatory reaction was similar, in many ways, to that in the meninges. There was an absence of eosinophil cells. The exudation contained, in addition to the pus cells, large cells like those in the brain, also plasma and epithelioid cells. Arthritis is a not uncommon complication of epidemic meningitis and, according to Adami and Nicholls,[67] Herrold[68] and others the meningococci have been isolated from the joints in these cases. Herrick[69] has added much valuable material to the subject of extra-meningeal infections with the meningococcus. The epidemic which he studied at Camp Jackson was of the septicemic type and was, of course, accompanied by a large proportion of such conditions.

Laboratory Diagnosis.—The examination of the spinal fluid is the most important procedure in making a diagnosis of meningitis. A brief statement of the theories most generally accepted as to the formation and circulation of the spinal fluid may be of interest. This is very thoroughly discussed by Cushing and Weed,[70] who believe that the cerebrospinal fluid is derived from two sources, the choroid plexuses of the cerebral ventricles, which derive the fluid from the blood by a process of filtration and secretion, and the perivascular systems of the nervous tissues, which pour the fluid waste-products of nerve activity into the subarachnoid spaces. The greater part of the spinal fluid is derived from the choroid plexuses of the lateral ventricles.

From the lateral ventricles the fluid passes through the foramen of Munro into the third ventricle and thence by the aqueduct of Sylvius into the fourth ventricle. From the fourth ventricle it passes through the foramen of Magendie (believed by some to be an artefact) and the foramina of Luschka into the subarachnoid cisterna about the cerebellum. Thence it passes downward along the subarachnoid space of the spinal canal and upward over the cerebrum.

The drainage of the spinal fluid has been the subject of diverse theories. Key and Retzius,[71] and Quincke[72] believed that the Pacchionian granules were the path of absorption. At an earlier date than the paper by Cushing and Weed, previously mentioned, Cushing believed that the spinal fluid entered the venous sinuses through valve-like openings. Mott[73] suggested that the spinal fluid was taken up by the cerebral capillaries by a process of diffusion and osmosis; Dandy and Blackfan[74] thought the mechanism of absorption was a diffuse process of the whole arachnoid. Weed[70] concluded that the fluid was returned to the general circulation in two ways—by the process of filtration by arachnoid villi into the cerebral sinuses, this being the most important means, and by a drainage of the fluid into the lymphatic system, this being the only way in which fluid escapes from the spinal subarachnoid space.

The normal amount of cerebrospinal fluid is probably from 100 to 150 c.c. The secretion of the choroid plexus is believed to be increased by the action of several drugs—ether and other inhalation anesthetics, pituitary extract, pilocarpin, choroid extract and posterior-lobe secretion of the hypophysis—and to be decreased by thyroid extract. The uninjured choroid plexus has been considered very effective in keeping out of the cerebrospinal fluid most substances in the circulating blood, as the agglutinins of typhoid fever, the toxin of tetanus, hemolytic amboceptor, and drugs, such as potassium iodide, salvarsan, etc. However, Park has shown that when a horse has a high antitoxin content in the blood, about 1 per cent. as much will be found in the spinal fluid, and it has recently been demonstrated by Sacks, Benedict, Dercum[75] and others that there is an appreciable quantity of arsenic in the spinal fluid after it has been administered intravenously in patients suffering from cerebrospinal lues.

Most poisons are far more toxic when injected into the cerebrospinal space than when reaching the nervous system through the blood stream.

A routine examination of spinal fluid should include a study of the cytology—an estimate of the number and kind of cells, not necessarily a cell count—the bacteriology, chemistry, albumin, globulin and sugar content, and in case of suspected tuberculous meningitis, animal inoculation. When syphilis is suspected, a Wassermann test should be done. In some instances a gold chlorid determination throws additional light on the diagnosis, especially in syphilitic conditions. It also assists when the diagnosis rests between poliomyelitis and indeterminate fluid changes in meningism. Complement fixation with the meningococcus antigen and the spinal fluid or blood serum in suspected cases of epidemic meningitis, when the organism does not grow, may be of value. Although reports of complement fixation in a few cases of epidemic meningitis have been reported, the subject has not been thoroughly studied, and it is now under investigation at the Research Laboratory of the Department of Health, New York City.

It may be of value to preface the more detailed discussion of the spinal fluid in epidemic meningitis by a brief discussion of the findings in other meningeal conditions. Cytology—the value of the cell count—has, we feel, been greatly over-estimated. Indeed, we think that the reliance placed on the cell count has resulted in many workers contenting themselves with it and failing to go on with the chemical examination, which is of at least equal importance. The exact cell counts have very little diagnostic value, as they overlap for a wide range in the clear fluids of poliomyelitis, epidemic encephalitis and tuberculous meningitis, and, indeed, in the rare cases of clear fluids in epidemic meningitis. In the clear fluids with a very slight increase in cells, such a count is not sufficiently accurate to be absolutely relied on for an exact diagnosis. In the case of cloudy fluids it is evident that the cells are very greatly increased and the approximately exact number is not of importance either in the diagnosis or prognosis. We find it satisfactory to centrifuge clear or slightly cloudy fluids for an hour at high speed. Smears made from the sediment are stained with the Ziehl-Nielsen stain for the tubercle bacillus in the case of clear fluids, and both the Ziehl-Nielsen and the Gram stain in the case of slightly cloudy fluids. From the stained sediments, the number of cells can be estimated as not increased when there is no more than one cell to four or five fields, or as slightly, moderately, greatly or very greatly increased. From the stained sediment, also, the percentage of mononuclear and polymorphonuclear cells and the presence or absence of bacteria may be noted. Cloudy fluids may be allowed to stand and a smear made from the sediment, but it is better to centrifuge for about 15 minutes, especially with the fluids of cases of meningitis under

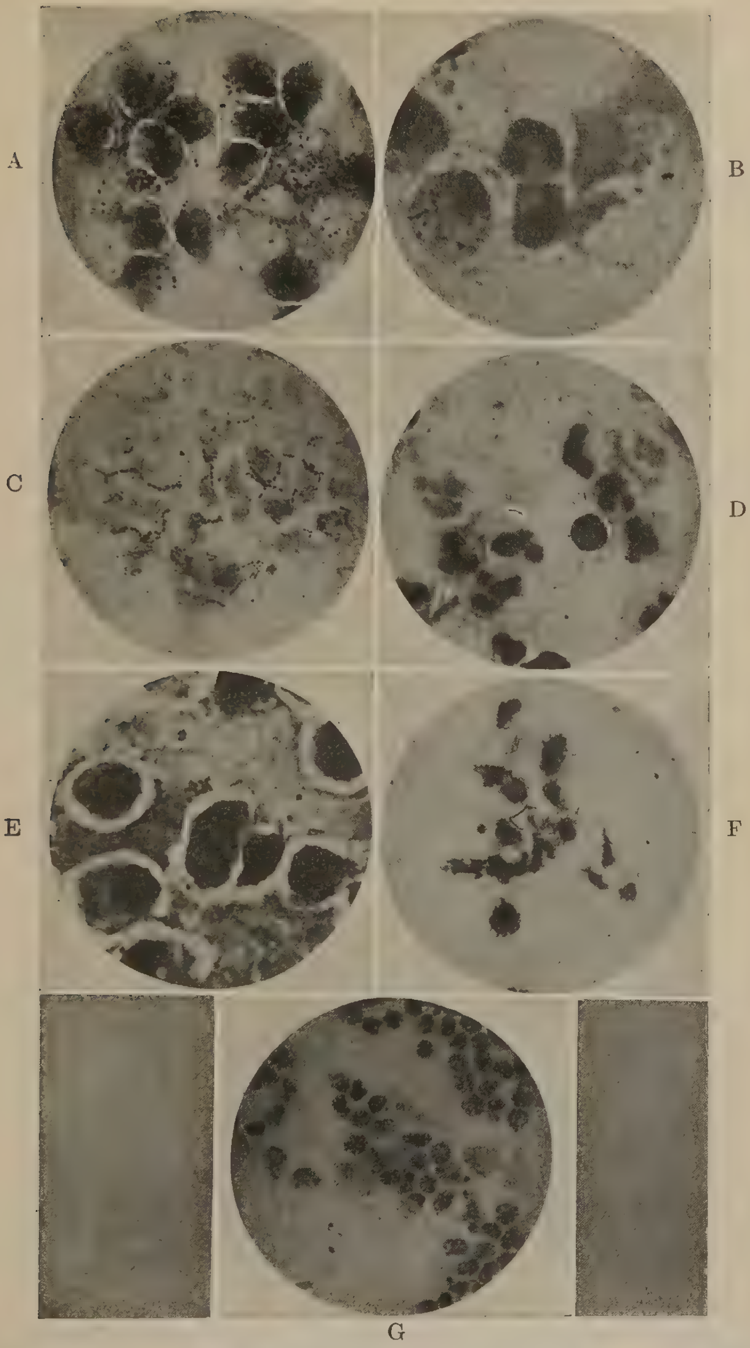

FIG. 72.—Microphotographs of sediments of spinal fluids. A, Epidemic meningitis. B, Pneumococcic meningitis. C, Streptococcic meningitis. D, Influenzal meningitis. E, Staphylococcic meningitis. F, Tuberculous meningitis. G, Poliomyelitis.

treatment, thereby obtaining in the sediment as many organisms as possible, if any are still present, because the further treatment depends largely on whether or not the culture is sterile. The smear of distinctly cloudy fluids should be stained by the Gram method. It is never safe to use the methylene blue stain and rely on the morphology for making even a tentative diagnosis, as the pneumococcus, streptococcus and staphylococcus may be intracellular and the meningococcus is frequently extracellular. A positive diagnosis should wait upon the result of the culture, as it sometimes happens that pneumococci or streptococci in spinal fluids decolorize very readily. Cultures from the sediment should be made on media suitable for a differentiation of the organism suspected to be present; and in the case of apparently sterile fluids, on glucose ascitic agar or on "chocolate" agar—the media most suitable to the growth of the meningococcus.

In normal fluids and in meningism the cells are not increased, and an average of not more than one cell to four or five fields or a cell count of 10 per cubic millimeter will be found. Very rarely the cells are somewhat increased in meningism.

In poliomyelitis and epidemic encephalitis, the cells are usually slightly to moderately increased, though sometimes the increase is very great. The type of cell is in most cases the mononuclear. In a few cases there is an excess of polymorphonuclears. It was once thought that an excess of polymorphonuclears was the rule early in poliomyelitis and that the mononuclears made their appearance later. Further study has shown that the excess of the polymorphonuclears belongs to a type of reaction, not to a stage of the disease. Polyform and endothelioid cells are often found.

In tuberculous meningitis the cells as a rule are moderately to greatly increased, and the mononuclears predominate up to 95 per cent. In a few instances the fluid is hazy with a preponderance of polymorphonuclears. In such fluids the tubercle bacilli are usually fairly numerous and easy to demonstrate.

In a meningitis due to the meningococcus or other pyogenic organisms, the cells are usually enormously increased with the polymorphonuclears predominating up to 98 per cent. In four or five instances only have we seen very early in an epidemic meningitis a fluid with so few cells as to be nearly clear, although organisms were present. In a few cases of meningitis due to other organisms there have been but few cells with an overwhelming infection—a smear from the fluid resembling that of a pure broth-culture of the organism.

Chemistry.—The chemical tests that we use are the nitric-acid-ring test for albumin and the Noguchi butyric-acid test* for globulin. The albumin and globulin practically always run parallel, but they serve as a check on each other. The small amount of albumin and

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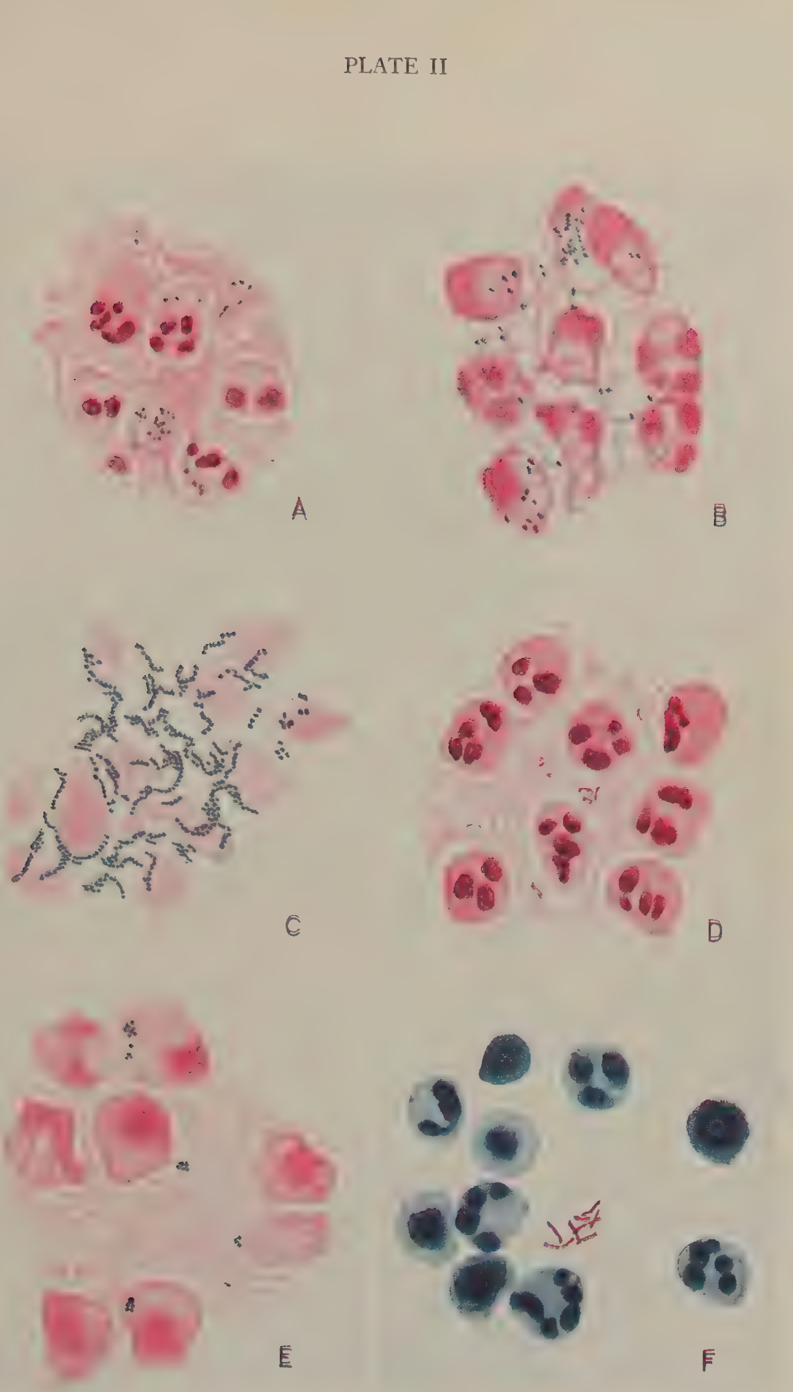
* This test consists in adding to two parts of spinal fluid five parts of 10 per cent. butyric acid in normal saline, boiling, adding about one part of normal sodium hydroxid and boiling again. Too much sodium hydroxid spoils the test by redissolving the globulin.

PLATE II



Colored drawings from sediments of spinal fluids: A, Epidemic meningitis; B, pneumococcic meningitis; C, streptococcic meningitis showing large number of organisms and poor cellular reaction; D, influenzal meningitis; E, staphylococcic meningitis; F, tuberculous meningitis—showing numerous organisms and high percentage of polymorphonuclears.

globulin present in normal fluids is marked as ±. This albumin is considered by Anglada[76] to be serum globulin, serum albumin being found only in cases where there is an inflammatory reaction. The globulin test shows with normal fluids a slight opalescence; with pathological fluids flocculi, finer or coarser, throughout the fluid. The signs, +, +1, ++, ++1, +++, ++++, represent increasing amounts and serve as a rough quantitative estimation. The presence of glucose is tested by using an equal amount of Fehling's solution and spinal fluid. It is marked as −, +, +1, ++, +++, with regard to the speed and the amount of the reduction, the +++ being the marking for a normal fluid. The globulin reaction and the reduction of Fehling's should not be read for half an hour.

Fluids from cases of meningism give, with rare exceptions, a normal chemistry.

In poliomyelitis and epidemic encephalitis, fluids usually show a slight to a moderate increase in the albumin and globulin and a normal or increased reduction of Fehling's, but in a few instances, especially those showing the syndrome of Froin, the albumin and globulin are very greatly increased, and the reduction of Fehling's is diminished probably on account of the excess of albumin present.

Fluids in cases of tuberculous meningitis usually show a larger amount of albumin and globulin than do poliomyelitic and epidemic encephalitic fluids. Early in tuberculous meningitis the reduction of Fehling's may be nearly normal, but as the disease progresses the reduction is usually diminished or absent. The statement has been made that a point of difference between fluids of poliomyelitis and tuberculous meningitis is that fluids from poliomyelitis reduce Fehling's, while fluids from tuberculous meningitis do not. This is not uniformly true. Almost 75 per cent. of tuberculous fluids show some degree of reduction of Fehling's, and a very small number of poliomyelitis fluids show a slightly diminished reduction. However, it may be safely stated that a considerable diminution in the reduction of Fehling's in dealing with a clear fluid, together with an increase in mononuclear cells and albumin and globulin, is very reliable evidence that the case is one of tuberculous meningitis.

In fluids from the purulent meningitides the albumin and globulin are usually moderately to very greatly increased. Early in any of the cases of purulent meningitis, there may be a fairly good reduction of Fehling's which disappears as the condition becomes worse.

A normal spinal fluid is perfectly clear, and when withdrawn with the patient in a horizontal position, it flows slowly, drop by drop, perhaps 10 to 15 drops to the minute. The rate of the flow varies with the caliber of the needle used and with the resistance offered by the patient. Struggling and crying increase the flow.

In pathologic conditions the fluid is practically always increased in amount. It may be either clear or cloudy.

A clear fluid increased in amount may indicate tuberculous meningitis, poliomyelitis, epidemic encephalitis, meningism, syphilitic involvement of the central nervous system, brain tumor, or rarer neurologic conditions. A clear fluid occurs very rarely in epidemic meningitis within the first 24 hours of the disease. A slightly cloudy fluid is sometimes found in rather acute cases of tuberculous meningitis and in poliomyelitis.

A cloudy fluid usually indicates (with the above exceptions) an invasion of the meninges by the meningococcus or some other pyogenic organism.

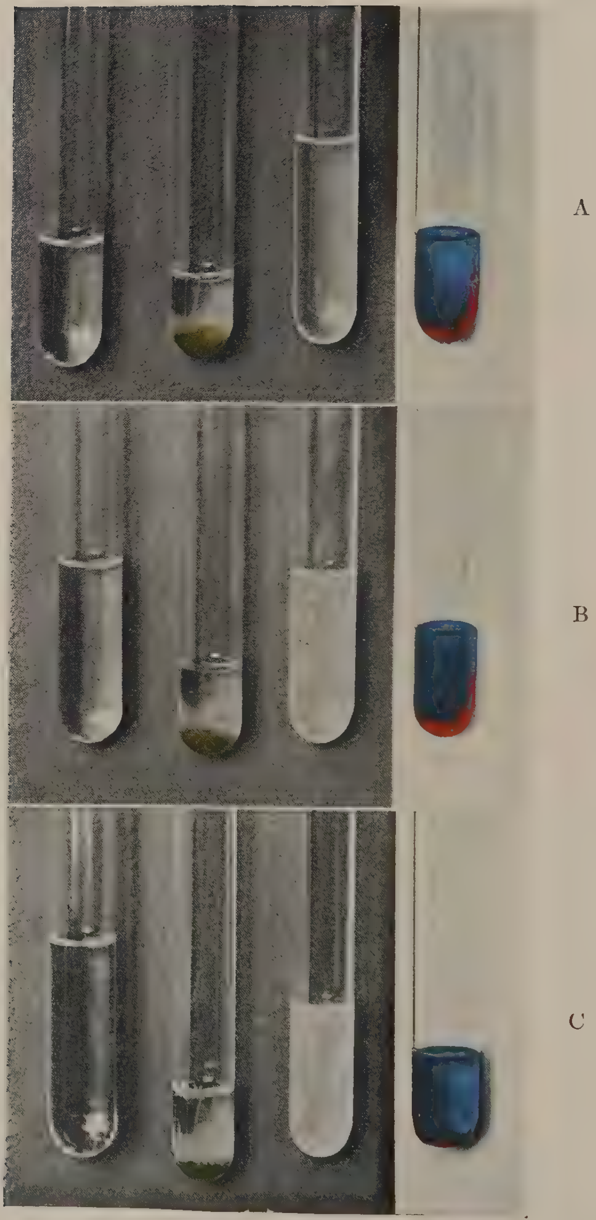
In epidemic meningitis the fluid escapes under increased pressure unless it is cut off by adhesions at the base of the brain or along the cord, or unless it is too thick to flow readily through the needle. Sometimes during treatment the amount of fluid is very small or there may be a dry tap, and yet the serum runs in readily. This will be discussed more fully under treatment. The fluid is usually cloudy, varying from a slight haziness to a thick purulent fluid, sometimes of a ropy or gelatinous consistency. Very rarely in cases seen within the first 24 hours the fluid is clear, particularly in fulminating cases. In cases seen later, that are clearing up spontaneously, the fluid may be only slightly cloudy.

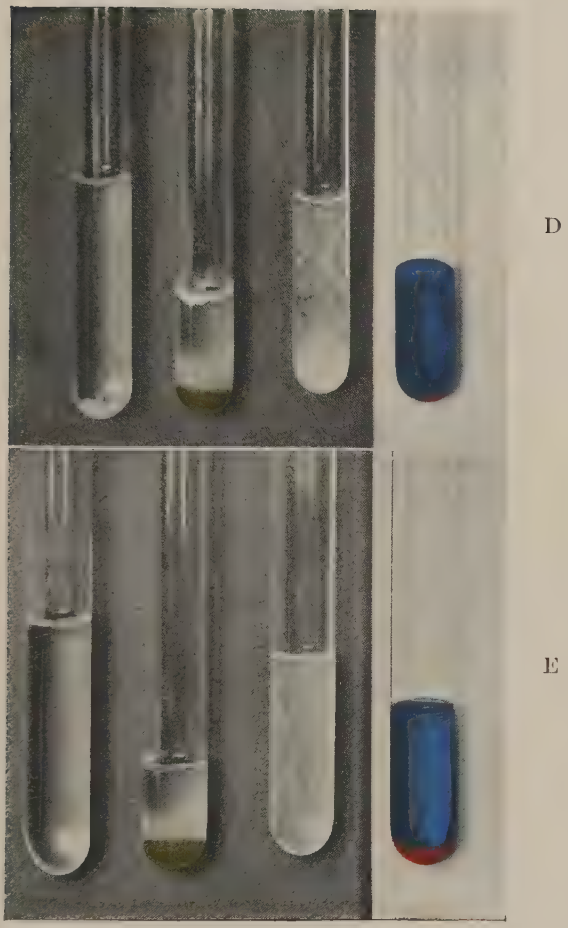
We have seen and examined clear fluids in but a few cases of epidemic meningitis, and these were punctured within the first 24 hours. Some equally early fluids are cloudy. In one case, E. G., puncture within the first 24 hours showed a very slightly hazy fluid. Table 5 shows results of examination in two cases in which the fluid was clear.

Occasionally early cases of any form of purulent meningitis will show a perfectly sterile fluid in the first and even in later punctures, although the cytology and chemistry indicate a meningitis. These cases should be treated as meningococcic meningitis until the specific organism develops, because it is most desirable to give anti-meningitis serum early if the case is one of epidemic meningitis, and in all other forms any treatment is so unsuccessful. In most fatal cases, not dying from complications, the organisms persist in the fluid though they do not necessarily increase greatly in number.

As to the chemistry, the albumin and globulin usually show a moderate to great increase. This tends to decrease as the case clears up, but never reaches normal before the serum treatment is stopped. This is partly because the inflammation itself takes a long time to subside and partly because the serum tends to keep up an asceptic meningitis. In some favorable cases, marked chemical changes persist to the end. The sugar content, as shown by the reduction of Fehling's, bears, in most instances, a very striking relation to the progress of the case. Early in any case of purulent meningitis there may be a fairly good reduction of Fehling's but this disappears as the condition becomes worse. If a case of epidemic meningitis is mild the reduction may remain nearly normal all through the disease. On the other hand, in most cases it disappears at the height of the disease, to return as the patient improves. We have come to look upon the reduction of Fehling's as being of great prognostic value.

PLATE III





Chemistry of spinal fluids showing albumen, globulin, and reduction of Fehling's in order. First tube is the fluid.

A, Normal fluid—albumen ±, Globulin ±, Fehling's +++.

B, Poliomyelitis fluid—Albumen ++, Globulin ++, Fehling's +++.

C, Tuberculous meningitis—Albumen +++, Globulin +++, Fehling's +.

D, Epidemic Meningitis (early)—Albumen ++++, Globulin ++++, Fehling's trace.

E, Epidemic meningitis (same case as (D) later case is recovering)—Albumen ++1, Globulin ++1, Fehling's ++.

In cases in which the albumin and globulin are still greatly increased at the time of recovery, as mentioned previously, the reduction of Fehling's may be absent. However the prognostic value of the reduction of Fehling's holds in the majority of cases. It has been conclusively proved that the reducing substance in the spinal fluid is glucose. It was formerly considered by some workers to be pyrocatechin.

The Lange colloidal gold test has been used for some time, chiefly in the study of the spinal fluids in syphilitic patients; in such conditions its diagnostic value is very great. The opportunity was offered us through the courtesy of Dr. George Draper in the summer of 1916[79] to have this test performed on many fluids from various conditions. The results with a brief description of the technique are given in the following paragraphs.

Lange Colloidal Gold Reaction.—The Lange test depends on the fact that pathologic spinal fluids in various dilutions will precipitate a colloidal gold solution in the presence of an electrolyte. The quantity of electrolyte used is sufficient to hold the proteins of the spinal fluid in solution, but not to cause, of itself, precipitation of the colloidal gold. The dilutions of spinal fluids in which these color changes occur have a certain degree of specificity in various diseases, and if arranged in series, can be correlated to certain "curves" of color changes. These color changes can then be used as a diagnostic method in examining spinal fluids.

The test is performed as follows:*

Into the first of 11 test tubes, place 0.9 c.c. of fresh, sterile 0.4 per cent. NaCl solution. Into each of the remaining 10 tubes, put 0.5 c.c.

Now add to the first tube 0.1 c.c. of the spinal fluid to be tested. Mix well, transfer 0.5 c.c. of the resultant 1:10 dilution of spinal fluid to the second tube. Again mix thoroughly and transfer 0.5 c.c. of this dilution to the third tube. Proceed in this manner up to and including the *tenth* tube. The 0.5 c.c. removed from the tenth tube is discarded. By this method, a series of dilutions of the spinal fluid is secured in geometrical progression, ranging from 1:10 to 1:5120. Now add to each of the 11 test tubes 2.5 c.c. of the prepared and standardized colloidal gold solution. Shake each tube thoroughly and set aside for reading after 12 or 15 hours. The eleventh tube serves as a salt control because it contains no spinal fluid.

Reading the Test.—A normal spinal fluid shows no color change as the gold is not precipitated and to this unchanged color is designated 0. Thus a normal curve would read "unchanged in color in all 11 test tubes" or

1	2	3	4	5	6	7	8	9	10	11
0,	0,	0,	0,	0,	0,	0,	0,	0,	0,	0.

---

* After the method of S. R. Miller, N. D. Brush, etc., published in the Bulletin of the Johns Hopkins Hospital, Baltimore, xxvi, No. 298 (December, 1915). In the original quotation, double the quantities mentioned herein were indicated.

Complete decoloration of the gold solution is designated by the number 5, and a fluid that precipitated the gold in all dilutions would give a curve reading "complete precipitation in all tubes," as 5, 5, 5, 5, 5, 5, 5, 5, 5, 5.

The color changes between normal red and the water-clear appearance in complete precipitation are numbered in order as follows:

Normal or brilliant red orange 0; red blue 1; lilac or purple 2; blue 3; pale blue 4; complete decolorization 5.

A normal fluid causes no color change and gives a curve reading

0, 0, 0, 0, 0, 0, 0, 0, 0, 0.

A typical paretic fluid shows complete precipitation in the first five dilutions, and the reading is

5, 5, 5, 5, 5, 3, 1, 0, 0, 0, 0.

A typical luetic fluid shows partial precipitation in the third and fourth dilutions grading off to normal in the last four, or,

0, 1, 2, 3, 3, 1, 0, 0, 0, 0.

A typical meningitis curve shows complete precipitation only in last dilutions and reading is

0, 0, 0, 1, 1, 2, 4, 5, 3, 1.

These readings are given in Fig. 73 and are the curves obtained by Doctors Miller, Brush, *et al.*, of Johns Hopkins Hospital as previously referred to. The readings obtained at this laboratory were as follows:

	Reading										Number of fluids	Chart
Normal	0	0	0	0	0	0	0	0	0	0		
Epidemic meningitis	1	1	1	1	2	3	1	1	0	0	57	II
Tuberculous meningitis	1	1	1	2	3	3	2	1	0	0	40	III
Poliomyelitis	1	1	2	2	1	0	0	0	0	0	109	IV
Streptococcus meningitis	1	1	1	1	1	2	3	31	2	1	2	
Staphylococcus meningitis	1	1	1	2	3	2	1	1	0	0	1	
Pneumococcus meningitis	1	1	1	2	2	3	3	2	1	0	6	

The 57 epidemic meningitis fluids are taken from patients in all stages of the disease. Some were obtained before serum had been administered; others, as late as the ninth lumbar puncture. It was found that the curve for each case was practically constant at whatever stage the fluid was withdrawn. Neither the clinical condition of the patient nor the fact that serum had been given affected noticeably the curve in any one case, though as many as four fluids were examined in some of the cases. It is to be noted that the routine albumin and globulin tests in these cases also remained practically constant. Had

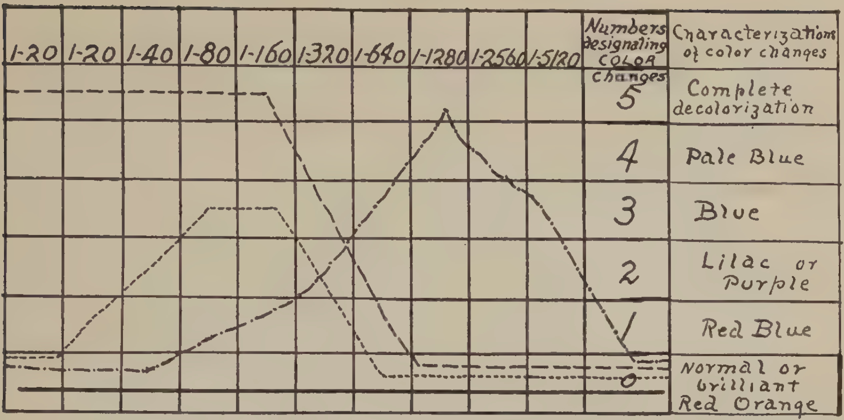


FIG. 73.—Curves of cases of paretic, meningitic and syphilitic spinal fluids, reported in Bulletin Johns Hopkins Hospital, 1915, 26, 298. Dilution of fluids in each instance as shown in figures at the top of the chart, 1:10, etc. Paretic, 5555531000; syphilitic, 0123321000; meningitic, 00011245210.

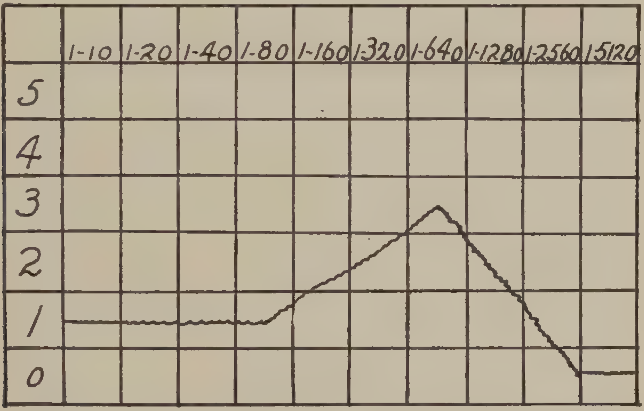


FIG. 74.—Epidemic meningitis, 57 fluids, 11112231100.

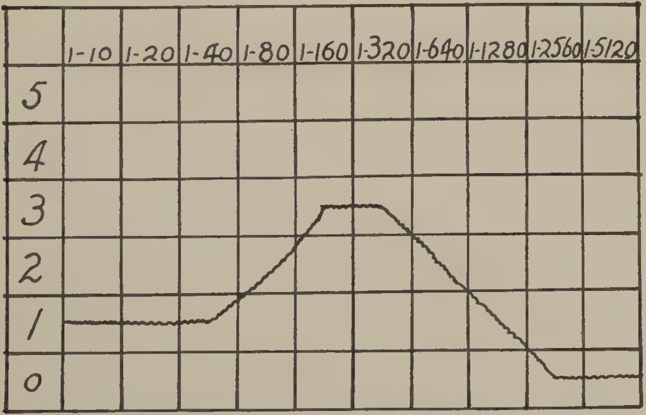


FIG. 75.—Tuberculous meningitis, 40 fluids, 1112332100.

the albumin and globulin content changed, as it frequently does in the series of fluids taken in the same case, it is probable that the gold chlorid curve would have changed also. Therefore, it must not be inferred that the gold chlorid curve is always constant throughout the course of the disease.

The 57 epidemic meningitis fluids gave a practically constant curve as did the fluids of tuberculous meningitis and other purulent meningitides.

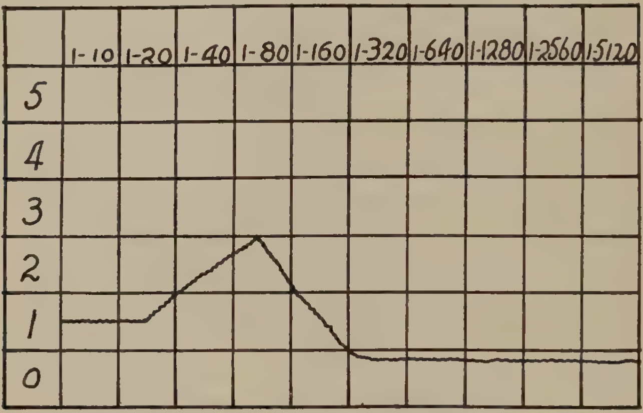


FIG. 76.—Poliomyelitis, 109 fluids, 1122100000.

The 109 poliomyelitis fluids, however, fell into practically six distinct curves, the one given in the chart being the average of the six, which read as follows:

1 1 2 2 1 0 0 0 0 0
1 1 3 3 2 1 0 0 0 0
1 1 1 2 2 1 0 0 0 0
1 1 2 1 1 0 0 0 0 0
1 1 1 1 0 0 0 0 0 0
1 1 2 1 0 0 0 0 0 0

Average reading was approximately 1, 1, 2, 2, 1, 0, 0, 0, 0, 0.

It will be observed that our meningitis curves differ materially from the curves given by Miller and Brush. However, our curves were obtained from a fairly large number of cases. It will also be noted that the various types of meningitis give practically the same type of curve.

In studying the curves of fluids taken in cases in which the diagnosis lay between meningism with slightly abnormal fluids, and non-paralytic poliomyelitis with fluids showing less than the usual amount of change, the curve gave us considerable help in several instances, the fluids in meningism giving a normal curve, while those of poliomyelitis showed changes. It may be that this reaction differentiates between serum globulin and serum albumin. According to Anglada,[76] serum globulin is the albuminous product present in normal spinal fluids, which, it is conceivable, may be increased under certain conditions; whereas serum albumin, he considers, is found only when a true inflammation is present.

Quantitative chemical studies on fluids of various kinds were made during the summer of 1916.[79] While the work was not as complete as might have been desired, the results are of interest in view of the comparatively little work that has been done along this line.

Table 7.—Quantitative Chemical Studies of Spinal Fluids

Diseases		Milligrams per 100 c.c.					Per cent.
		Total nitrogen	Non-protein nitrogen	Urea nitrogen	Creatinin	Creatin	Sugar
Poliomyelitis....	Median....	22.57	15.71	12.50	0.400	0.405	0.0613
	Limits...	34.00	24.78	26.60	0.9609	0.495	0.1063
		16.37	8.91	5.06	0.2730	0.190	0.0250
	Number of cases......	25	16	17	22	11	53
Epidemic meningitis.	Median....	47.25	21.93	9.25	0.476	0.704	Traces
	Limits...	250.00	136.25	53.28	0.595	.....	0.0628
		22.72	13.00	3.66	0.326	.....	Traces
	Number of cases......	30	23	26	5	1	23
Tuberculous meningitis.	Median....	25.88	13.88	7.14	0.626	0.649	Traces
	Limits...	34.50	17.25	14.18	0.7652	0.735	0.060
		20.86	12.82	4.54	0.4870	0.563	Traces
	Number of cases......	10	5	8	2	2	6
Normal spinal fluid.	Median....	15.30	13.69	8.23	0.365	.....	0.0815
	Limits...	22.72	22.38	12.05	.....	.....	0.0923
		9.67	13.68	5.35	.....	.....	0.0660
	Number of cases......	5	3	4	1	0	0

From a study of the findings in successive punctures in epidemic meningitis, it was shown that in cases in which recovery took place the nitrogenous elements decreased in amount and the sugar increased, while in cases resulting in death the opposite results obtained. These results bear out the rough quantitative estimation made in the routine examination.

Following is a table giving the brief characteristics of the various types of fluids in acute conditions.

TABLE 5.—RESULTS OF EXAMINATION OF TWO CLEAR SPINAL FLUIDS

		Case T. O.	Case M. H.
Amount in cubic centimeters		55	20
Appearance		Clear	Clear
Cytology		Cells slightly increased 50 per cent. polymorphs 50 per cent. monos	No increase
Bacteriology	Smear	Gram-negative cocci	
	Culture	Pure, giving gram-negative cocci	Same
Albumin		+	+
Globulin		+	+
Fehling's		++	+++

These two cases showed a very slight cellular reaction and changes in chemistry. Death occurred in both cases, in the first within 36 hours, in the second within 24 hours of the onset. In another case that we saw in a hospital, death also occurred within 48 hours of the onset. A positive culture was obtained. The patient in whom the fluid was slightly hazy recovered. The fluid findings are shown in Table 6.

TABLE 6.—FINDINGS IN SLIGHTLY HAZY SPINAL FLUID (CASE E. G.)

Amount in cubic centimeters		40
Appearance		Nearly clear. Fibrin web
Cytology		Moderate increase, 85 per cent. polymorphs
Bacteriology	Smear	Gram-negative cocci
	Culture	Gram-negative cocci
Albumin		+1
Globulin		+1
Fehling's		++

Netter and Debré say that in 75 out of 100 cases seen within the first 24 hours, the fluid is clear and there is an excess of mononuclears, though the cells are few and the organisms are usually numerous. From the few cases that we have seen during the first 24 hours of the disease, we cannot draw sufficiently definite conclusions to confirm or refute this statement. We have, however, seen several cases within this time which showed a well-marked cellular reaction, so that, so far as our experience goes, we would not be inclined to agree with Netter and Debré.

Flack[31] mentions 15 clear fluids out of 59. In only five of these cases were growths obtained, however, and no data is given as to the time of puncture or any of the other findings in the examination of the fluids. In the reports of Herrick,[77] and Landry and Hamley,[78] clear fluids with or without organisms are described early in the course, particularly in the septicemic type of meningitis. It is obvious that the fluid may be clear because there is an overwhelming infection to which the individual is unable to react or because the fluid is withdrawn before the reaction has developed.

The usual type of fluid, however, shows at the first puncture a varying degree of cloudiness, and the cells are 90 per cent. or more polymorphonuclears. The number of cells may run as high as 10,000 or 15,000 or even more. In addition to the polymorphonuclears and small mononuclears, in some fluids large mononuclears are seen apparently similar to those described by Councilman, Mallory and Wright as occurring in the meninges and brain tissue. As the patient improves, the fluid becomes clearer with a decreasing number of cells, and the percentage of mononuclears increases; the organisms also decrease in number and become more and more intracellular. Finally, the cultures become sterile. A clearer fluid is not indicative of good prognosis unless it is accompanied by a decrease in the organisms with cultures finally becoming sterile.

Meningococci may be found early in varying numbers, and may be intracellular, extra-cellular or both. A culture is usually obtained, especially if the fluid is examined promptly. Forty-eight hours or more should be allowed for growth before the culture is pronounced negative. Occasionally degenerated organisms can be demonstrated in the smear while the culture is sterile. On the other hand, sometimes, especially early or late, when the organisms are too few to be demonstrated by smear, the culture will be positive. When the organisms are very few, the culture and smear should be made from the centrifuged sediment to secure the largest possible number.

If a case is clinically one of epidemic meningitis and responds to the antimeningitis serum, and if it has the spinal fluid of a meningitis even though organisms may not be demonstrated, I think it is fair to assume that such a case is one of epidemic meningitis.

Certain points in the examination of the spinal fluid of interest but of no great practical value, or that only duplicate steps already described, should perhaps be briefly mentioned.

There are several tests for globulin. The Ross-Jones test is quite generally used. It consists in layering concentrated ammonium sulphate solution and spinal fluid—1 c.c. of the latter being carefully floated on 2 c.c. of the ammonium sulphate. If a ring of hair-like fineness is obtained after three minutes, the reaction is considered to signify a globulin excess. The thickness of the ring and the time of its appearance should be taken into consideration in marking the reactions. The Pandy reaction is preferred by some workers. The reagent consists of carbolic-acid solution prepared by adding from 80 to 100 c.c. of pure carbolic acid to a liter of distilled water. It is thoroughly shaken and placed in the incubator for several hours. It is then allowed to stand at room temperature for several days. The supernatant liquid is then removed and used as the reagent. A drop

TABLE 8.—CHARACTERISTICS OF THE VARIOUS FLUIDS

Meningeal condition	Pressure	Amount, cubic centimeters	Appearance	Cytology	Bacteriology	Albumin	Globulin	Fehling's solution	Animal inoculation
Normal..............	Normal	5–10	Clear	Very few cells	Sterile	±	±	+++	Negative
Meningismus.........	Increased	A. 30–40 M. 100	Clear	Very few cells	Sterile	±	±	+++	Negative
Poliomyelitis and epidemic encephalitis.	Increased	A. 25–50 M. 100	Clear; sometimes slight fibrin web	Rarely polynucleosis; usually lymphocytosis up to 95 per cent. Endothelioid and polyform cells	Sterile	+ to ++++	+ to ++++	+++ Rarely ++	Negative
Tuberculous meningitis.	Increased	A. 30–50 M. 120	Clear fibrin web	Lymphocytosis up to 95 per cent. Rarely polynucleosis	Tubercle bacilli	++ to ++++	++ to ++++	– to +++ – in 25 per cent.	Tuberculosis in four weeks
Epidemic meningitis...	Increased	A. 20–50 M. 120	Cloudy	Polynucleosis up to 98 per cent.	Meningococcus	++ to ++++	++ to ++++	+++ to – according to severity and stage	
Meningitis due to other organisms	Increased	A. 20–50 M. 100	Cloudy	Polynucleosis up to 98 per cent.	Infecting organism	++ to ++++	++ to ++++	– may be + or even +++ early	

A.—Average. M.—Largest amount observed.

In any purulent meningitis with a very thick exudate the amount of fluid may be greatly decreased.

of centrifugalized spinal fluid is allowed to trickle down the side of a watch glass full of the reagent, and the reaction is read from the resulting cloudiness or precipitation.

The index of reduction of potassium permanganate is higher in a fluid from a meningitis than in a normal fluid, and it is said to become lower as the patient improves. It has not found very general favor.

The ninhydrin tests have been suggested as of diagnostic value in tuberculous meningitis. A study of this reaction showed that it ran parallel with the albumin and globulin content and had no additional value.

The reaction of the spinal fluid has been studied by Levinson[80] who finds that the normal alkalinity, using methyl red as an indicator, is from 2.0 to 2.4. In epidemic meningitis it is lower, from 0.7 to 1.3. In tuberculous meningitis it is unchanged.

The cryoscopic point of normal spinal fluid is from 0.54° to 0.6°, and in cases of acute meningitis and in tuberculous meningitis is lower, about 0.46°. This would be consistent with the decrease in chlorids which is reported in the spinal fluid of acute meningitis.

The pressure of the spinal fluid is normally from 30 to 50 mm. according to Quincke[72] and from 120 to 180 mm. according to Koenig. In meningitis, this is greatly increased. Sladen[81] reports a pressure of 650 mm. and an average pressure of 327 mm. The lowest recorded on first puncture was 160 mm. Heiman and Feldstein[1] report a minimum pressure of 40 mm. in an infant suffering from meningitis, and a maximum of 510 mm. The pressure is greatly changed by coughing, straining and change in position.

The precipitin reaction of Vincent and Bellot has already been referred to under bacteriology.

Blood.—The blood picture in epidemic meningitis is a leukocytosis with a polynucleosis. According to Koplik[82] there are over 25,000 leukocytes in more than half the cases. Counts of 20,000 to 50,000 seem to be common except in chronic cases in which the count may become normal.

Until the occurrence of meningitis in the army, blood cultures had not been made in a very systematic way. Elser and Huntoon[46] in the New York epidemic of 1904 to 1906 found positive cultures in 11 out of 41 cases. The question of blood cultures was studied very carefully under Major Herrick's[69] direction at Camp Jackson where a large number of cases of the septicemic type of meningitis occurred. Barber and Fleming[83] in a series of 15 cases obtained 12 positive cultures—80 per cent. Baeslack[84] and others obtained positive cultures in 36 per cent. of early cases. Baeslack comments on the necessity of taking large amounts of blood because in mild cases the organisms are few. He recommends 15 to 20 c.c. of blood in each bottle of 80 to 100 c.c. of meat infusion bouillon, salt-free, containing 1 per cent. glucose and 10 per cent. serum water. The medium should be warmed immediately before use. Subcultures are made at 24 hour intervals on 1 per cent. glucose blood agar plates. Positive cultures appear in from

48 to 96 hours. Negative cultures should not be discarded until after five days have elapsed. It must be remembered that the cases at Camp Jackson contained a very large proportion of the septicemic type, in which it would be expected that a high percentage of positive blood cultures would be obtained. At other camps where this type of meningitis was not prevalent, the percentage of positive blood cultures was much lower.

Stone and Truitt[36] report: "Positive blood cultures were obtained in a larger percentage of patients with petechiæ, while negative blood cultures were as a rule obtained in those patients not manifesting petechiæ."

Maxcy[85] reports an interesting experience at Camp Beauregard. "Blood cultures were done on 27 patients suspected of being abortive cases of meningococcus infection, all with negative results. In none of these cases were petechiæ present." This raises the question as to whether abortive cases of meningitis are very common and also how they may be diagnosed.

The agglutinating power of the patient's serum has been studied to some extent. This power varies a good deal both as to the time when it first makes its appearance and as to its persistence. It is of most value when carried out with the patient's own strain of organism. Hence, its diagnostic value is not great.

The opsonic index of the serum is of little diagnostic value on account of the spontaneous phagocytosis shown by many strains of the meningococcus and the difficulty in making sharply defined readings of the results.

Complement-fixation tests with the patient's serum and a meningococcus antigen have been reported on favorably by a few workers.

The presence of the meningococcus in the naso-pharynx of a patient supposed to be suffering from epidemic meningitis when the organism cannot be cultivated from the spinal fluid would add considerable evidence to the diagnosis.

The urine is in no way diagnostic. It usually gives the findings of an acute infection. According to Hutinel and Voisin,[86] albuminuria is rare, but sometimes there is a true nephritis, and rarely the urine is bloody. The diazo reaction is less frequent than in tuberculous meningitis but indicanuria is common and, according to Campagne, has some relation to the severity of the case. Glycosuria occasionally occurs but is usually transitory.

Retention is not uncommon, and in cases of cystitis the meningococci are sometimes found in the urine. Netter and Debré state that a polyuria sometimes occurs. This has not been noted in our cases.

Clinical Types.—Many writers on epidemic meningitis go to considerable pains in classifying the clinical types. When one remembers that as in other infectious diseases bacteria of varying virulence attack individuals of varying resistance, it is easy to see that the resultant of these two varying forces will show an almost endless number of forms, depending on the virulence and localization of the infection, and the age, anatomical peculiarities and the resistance of the host. It must be borne in mind that the meningococcus may invade the blood stream and produce a fatal septicemia without a meningitis developing. Such a condition lies within the range of the present discussion though it is not, of course, a meningitis. Perhaps it is most convenient to make the following divisions:

Acute Forms.—These consist of: (1) Ordinary acute forms of greatly varying degrees of severity, in which the patient is well on the road to recovery or is dead within from 10 days to two weeks. Some of these cases may be very mild, and are often classed separately under the term abortive.

2. Fulminating, in which death occurs within 72 hours, with or without a cellular reaction in the spinal fluid.

3. Septicemic type, in which the septicemia is a more striking feature than the meningitis. Until recent years this form has been comparatively rare. At certain of our army camps in 1917 to 1918, notably at Camp Jackson, this type has been the prevailing one. Dopter[87] and Netter[88] call attention to the greater frequency of this type in France of late and consider that it may have some relation to the change in the type of organisms Type *A* (Gordon's I and III) which had previously been more common, having been superseded by Type *B* (Gordon II and IV). Adequate proof of such a relation has not been established, however. The septicemia may clear up or proceed to a fatal termination without the meninges being involved. Such cases have been described by Andrewes,[89] Netter,[88] Herrick,[69] Morgan[90] and others. In the majority of instances signs of meningitis are present at some time during the illness.

Chronic Forms.—(1) Ordinary chronic form, in which the disease lasts three weeks or more before there is a decisive change for the better or worse. These cases often strongly resemble typhoid.

2. Relapsing form, with which may be included the relapsing meningococcus septicemia.

3. Form in which the process becomes walled off either in the ventricle, producing a basic meningitis, or in pockets, forming the encysted or loculated meningitis.

The clinical manifestations of the disease depend to such an extent on the age of the patient that some writers make separate types for young children and aged people. The picture in children under two years is indeed quite different from that of older patients, and it is in these cases that posterior basic meningitis is most likely to develop.

It was at one time believed that the Gram-negative coccus occurring in cases of posterior basic meningitis was a different organism from that causing epidemic meningitis. Subsequent study has proved them to be identical. Posterior basic meningitis may, however, develop in the course of other purulent meningitides. We have seen one case in an adult which, at necropsy, proved to be due to the streptococcus.

Symptomatology.—The symptoms are due to various causes and may be grouped in various ways. They may be regarded as representing a general reaction to an acute infection plus the specific reaction due to the involvement of the meninges and the central nervous system. It is sometimes difficult to decide exactly which element produces a given symptom, the action of toxin resulting from the growth and autolysis of the meningococcus, the increased pressure of the spinal fluid, or the active inflammatory reaction in the meninges and nerve tissue. In the production of many of the symptoms, doubtless two or more of these elements play a part. Therefore, no attempt will be made to exactly classify symptoms as to their causation.

Since few patients give a history of direct exposure, it is difficult to decide on the incubation period. From the comparatively few cases in which there is evidence of direct contagion, it would seem to be short, on the average from three to five days. Our own cases, with one or two exceptions, confirm this view.

Incubation Period.—The onset is abrupt, with rare exceptions. There is seldom any history of exposure, direct or indirect. As a rule, no predisposing cause appears, as for instance a previous debilitating illness or trauma. Some claim that the attacks are frequently preceded by a catarrhal infection or coryza, and such a history seems logical in view of the fact that the meningococcus is found in the nasopharynx. Of course, in New York a large proportion of the people suffer to some extent from catarrh, and colds are common, but no special manifestation of these conditions has seemed to precede our cases of meningitis.

The attack is usually ushered in by intense headache and chills, followed by fever and vomiting. At times, the onset may be very abrupt. The patient rapidly becomes unconscious although he had been feeling well an hour or so previously. Occasionally the onset is gradual with general malaise.

A typical case of average severity will present the following picture. We are called to see a boy of four or five years. He lies on his side. The face is flushed, the head thrown back, the legs drawn up, and perhaps a few petechiæ are scattered over his body, or a herpetic eruption is on his lips. There is a history of a sudden onset about three or four days previously, with headache, photophobia, vomiting and constipation, fever and perhaps a chill of moderate severity. Vomiting and fever have continued and stiffness of the neck has developed in from 24 to 36 hours after the onset. On examining the child we find a temperature of perhaps 103 degrees (the history will show that it has been irregular since the onset), the pulse is usually a little slower than the elevation of the temperature would indicate, the respirations are irregular, the so-called Biot type. The child is irritable and resists attempts to examine him but it will be obvious that the neck is stiff, that Kernig's sign is present, and a Brudzinski may be demonstrated. Percussion of the skull over the lateral ventricle gives a hollow sound, and the skull seems tense to the percussing finger. The patellar reflexes are slightly exaggerated. The pupils are equal and at this stage may react to light.

Lumbar puncture yields a fluid under increased pressure and of varying degrees of cloudiness. A very purulent fluid has by no means a bad prognosis. Serum is given. The next day the case probably will be decidedly improved; the vomiting has ceased, the headache is less, the temperature is lower, the fluid is not so purulent. In a favorable case, after four daily lumbar punctures, the patient will be free from headache and vomiting, the temperature will be practically normal, and the fluid only slightly hazy and much less in amount. The stiffness of the neck is usually the last symptom to disappear.

The principal symptoms and physical signs to be considered in studying meningitis are the following:

1. Temperature, pulse, respiration.
2. Headache.
3. Stiffness of neck.
4. Kernig's sign.
5. Brudzinski's sign.
6. Convulsions.
7. Paralysis or paresis.
8. Mental condition; unconsciousness, stupor, delirium, irritability.
9. Gastro-intestinal condition; vomiting, diarrhea, constipation.
10. Bladder; retention, suppression.
11. Reflexes; normal, increased, diminished, lost; equal, unequal.
12. Eyes; pupils—equal, unequal, dilated, contracted, reaction to light. Nystagmus, strabismus, ptosis, conjunctivitis, iritis, keratitis, hypopion, disturbances of vision, diplopia, loss of acuity, etc.
13. Ears; hearing, discharge.
14. MacEwen's signs or bulging fontanelle.
15. Eruption; hemorrhagic, herpetic and miscellaneous.

Temperature.—The temperature curve in epidemic meningitis is characteristic, in that it is practically always irregular and has little relation to the prognosis. It varies greatly in different cases, and even in a given case it does not follow any particular course. The temperature at the onset is almost invariably elevated, from 102 to 105 degrees, and it ordinarily remains elevated usually with remissions every few hours during the course of the disease, falling by lysis as the patient improves. Rarely a case is practically afebrile throughout a long and tedious illness. Two of our most prolonged cases have belonged to this class. One patient had a slight elevation of temperature at the onset and again at the beginning of a relapse. He suffered a very long and serious illness but finally recovered. The other patient had a still longer course but was not so sick. His temperature was normal most of the time except for rises at irregular intervals and following the injection of serum. Marked morning remissions and evening exacerbations sometimes occur, resembling active tuberculosis. Indeed, marked and sudden changes in temperature occurring every few hours are unusually common in this disease, and an accurate idea of the temperature is obtained only if it is taken at least every four hours. Rarely the temperature may fall by crisis soon after the administration of serum. More often it falls gradually, the injection of serum being followed in from four to six hours by an elevation of 1 to 3 degrees due to the serum reaction, after which it falls to a point a degree or more lower than when the puncture was done. This is repeated from day to day until the temperature is nearly normal. During convalescence, it may rise a degree or two at times without any very appreciable cause. If the elevation lasts only a short time and does not occur too often, no attention need be paid to it.

Pulse.—The pulse is usually increased in rate, though often not in proportion to the temperature, is regular in rhythm and of good volume and tension. At first thought, one would expect it to be slow on account of the increased pressure, but this is only rarely the case. Indeed Sladen[81] has shown in a series of cases in which the intraspinal pressure was measured that the higher pressures had the more rapid pulse rates. Doubtless this is due to the center in the medulla being depressed following the stimulation since the increased pressure continues. Netter and Debré[2] and Heiman and Feldstein[1] comment on the sudden changes in the pulse rate that may occur while one is making the examination, the rate varying from 60 to 110 or 130. It does not seem that this can be very common, as we have not observed it. It has been our observation that the rate and quality of the pulse is a very good index of the degree of intoxication of the patient.

Respiration.—The respiration is often of the Biot type, showing marked variation in the rate and depth. The rate is usually increased in proportion to the temperature. In very severe cases, the Cheyne-Stokes type often develops near the termination.

Many of the symptoms may be grouped under sensory and motor disturbances, arising from the inflammation of the meninges and nerves.

Headache and Other Sensory Disturbances.—Severe headache is an almost constant symptom in patients old enough to indicate their sensations. It is often diffuse, but it may be localized in the occipital or frontal region. The pain is usually very intense. A measure of relief is afforded by lumbar puncture in most instances. Pains in the limbs, except following the injection of serum which frequently causes some pain in the legs, is not very common. There may be pains in the back, especially in the cervical region. Patients are frequently hyperesthetic and sensitive to light.

Hypertonicity of Muscles and Motor Disturbances.—One of the most marked and characteristic symptoms of the disease is increase in muscle tone. This shows itself in various ways: First, the *stiffness of the neck.* This is almost constantly present in patients over a year old. It varies from a slight anteroposterior stiffness to retraction with almost complete fixation of the head. The retraction may be so great that swallowing is impossible. Another manifestation of this hypertonicity is *opisthotonus*, which often develops in serious and prolonged cases, especially in posterior basic types. The *Kernig's sign* is a third manifestation. This was described by Kernig as follows: The patient was placed in a sitting posture in bed with the thighs at right angles to the body. When the sign was present, the legs were flexed at the knees. It is rather undesirable to require patients with meningitis to sit up, and the following modification is usually employed. With the patient lying on his back the thigh is flexed at right angles to the body, and an attempt is made to extend the leg at the knee. When complete extension is impossible the sign is present. Attempts to secure extension produce pain. This sign, unless well marked, has seemed to us of much less value than the stiffness of the neck. It is often absent or difficult to determine in young children, and few adults who are not very athletic fail to show some resistance to complete extension. The Kernig sign is usually equal on the two sides. To the same cause is doubtless due the Brudzinski neck and leg signs. The neck sign is the more valuable. Indeed, in young children it is often of more value than the Kernig or the stiffness of the neck. It consists in the flexion of the legs when the head is forced forward. The leg sign is shown in either of two ways. When one leg is forcibly flexed, the other may flex also—called the identical contralateral reflex—or it may extend—reciprocal contralateral reflex.

Convulsions are rather common in young children, but as they occur with so many other diseases they are not particularly diagnostic. In adults and older children, they occur only in the severest cases.

Paralyses are rare, but they may occur. They may be very fleeting. In one case there was a paralysis of the right arm that made its appearance, became complete and cleared up entirely in a space of 12 hours. In other cases it has been more persistent, remaining to some extent for years. Paralyses of the eye muscles are the most frequent. When hemiplegias occur one would expect a Babinski. Otherwise it is rare. We have never been able to see why many physicians, in discussing cases of meningitis, make more or less of a point of the presence or absence of this sign, when it is remembered that the Babinski is normal in children under two years of age. Otherwise it indicates a lesion of the upper motor neuron. We would not expect to get this in meningitis unless the underlying brain substance was involved more than is usually the case, or unless a hemorrhage had taken place. Tremor is pointed out by Hutinel and Voisin[86] and others as occasionally occurring, being either general or affecting certain groups of muscles particularly the tongue or the head.

Mental Condition.—The mental condition is subject to the widest variations. In rather mild cases, the mentality may be practically normal throughout the course except for some irritability and restlessness. In more severe cases active delirium may develop early, sometimes clearing up with the first dose of serum. In other cases, when the recovery is slower, it lasts longer and may recur at intervals. In unfavorable cases, the delirium is usually succeeded by stupor, progressing to coma. In the very severe acute cases, stupor followed by coma may appear within the first 12 to 24 hours. In the more chronic type of case which falls into the typhoidal state a low muttering type of delirium is frequently present at intervals especially at night. In one or two cases, one in particular being very prolonged, the patient on recovering had absolutely no recollection of the illness or the treatment. He simply remembered that he went to bed with a headache, although during his illness he seemed to have lucid intervals when he recognized his family and friends.

Insomnia is often a troublesome symptom.

Gastro-intestinal Symptoms.—Vomiting almost constantly occurs early in the disease and may be very persistent for the first 24 to 48 hours. It is generally not projectile in type though it is not often associated with nausea. It usually clears up with the institution of treatment, but in untreated cases it often recurs periodically. In cases running a chronic course, it may recur with slight exacerbations of the disease. Constipation is the rule and it is often very obstinate even during convalescence. Loss of sphincter control is rare except in very severe cases in coma.

Bladder Symptoms.—Retention is an occasional symptom, and from it cystitis may develop. This has, in rare cases, been shown to be due to the meningococcus. The retention usually is of short duration, but it demands careful attention. Incontinence rarely occurs except as a result of the retention or in very severe cases in which coma develops.

Reflexes.—The patellar reflex is often increased early, becomes lost as the disease progresses and returns during convalescence. It may, however, remain normal throughout the illness. The cutaneous reflexes are not of great value. The pupillary reflex will be discussed under eye symptoms. In our experience the reflexes have been usually equal on the two sides.

A recent writer has made a considerable point of the diagnostic value of the inequality of the deep reflexes. A study of his table of symptoms, however, shows that in only 13 of 208 cases did this inequality of reflexes occur (the Kernig and Brudzinski are not usually classed as reflexes, I believe), and curiously in 12 of these 13 cases the reflex on the right side was greater than that on the left.

MacEwen's Sign and Bulging Fontanelle.—An increased pressure in the lateral ventricles, especially in children after the closure of the fontanelle, is indicated by a change in the percussion note over the lateral ventricle. This change was first pointed out by MacEwen and constitutes a very valuable sign according to most observers. A description of the change is not easy. It shows itself by a feeling of greater elasticity of the skull to the percussing finger—as if it were under tension—as well as by the hollow character of the sound. Considerable experience is necessary to obtain proficiency in deciding on the sign. Some observers listen with the stethoscope against the center of the forehead. We have not used this method. In adults with thicker skulls the sign is more indefinite, but even here it is often of value. Before the fontanelle is closed, the use of the sign is not indicated but the absence or presence of a bulging fontanelle is an almost infallible indication of the state of pressure of the spinal fluid. It is not absolutely infallible because on several occasions a lumbar puncture has revealed increased pressure although the fontanelle did not bulge.

Eruptions.—Herpetic and hemorrhagic eruptions are the most frequent. Herpes, while varying in different epidemics, occurs more frequently than any other eruption except in the septicemic type of meningitis in which the hemorrhagic rash is nearly constant. While the herpetic eruption most often occurs around the mucous membrane of the lips, according to Netter,[2] it may occur in unusual locations, as the sole of the foot, or following the course of one of the nerves. It may become confluent and form extensive and painful ulcerations. It usually appears from the third to the seventh day and Netter remarks that it has no prognostic significance.

A fleeting erythematous rash appearing at almost any time during the disease, on any part of the body, is described by various observers.

The hemorrhagic eruptions vary greatly in their occurrence in different epidemics. In some of the older epidemics they were much more common than they have been more recently, for instance, in 1904 to 1906 in New York City and in our sporadic cases in which their incidence has been about 15 per cent. In the epidemics in the army camps where the septicemic type has prevailed, the percentage of occurrence has been very high, as would be expected. The hemorrhagic rash may be macular, petechial or purpuric.

Generally, the hemorrhagic rash appears early within the first 36 hours. Foster and Gaskell,[3] however, describe a macular rash which in their cases appeared with some regularity on the fourth day of the disease. The petechial and purpuric rashes vary greatly in their extent. They are often more abundant on the elbows, knees and other points of pressure. The petechiæ are usually bright red while the purpura are of a dark purplish color, but it is probable that they represent different degrees of the same process, and all variations in size and color may be observed. That they are closely associated with the presence of the meningococci in the blood is shown in two ways, first, by the fact that positive blood-cultures are obtained in a very large percentage of cases in which a hemorrhagic eruption is present and in but a small percentage when it is absent and, second, by the fact that meningococci have been isolated from the rashes. In other words, a hemorrhagic rash is almost constantly present in meningococcus septicemia with or without meningitis. An extensive hemorrhagic rash or one of long duration is associated with a serious type of the disease. On the other hand, many cases that respond very promptly to treatment show early a moderate number of petechiæ of various sizes. These rashes are described with beautiful illustrations by Foster and Gaskell.[3] Eruptions both purpuric and hemorrhagic are more infrequent in very young children than in older patients. It must not be forgotten that a hemorrhagic rash may occur in any other form of septicemia and is therefore not pathognomonic of a meningococcus infection.

Most of the conditions relating to the eye and ear seem to belong to complications rather than symptoms and are described under that heading.

The foregoing description shows the symptoms that occur in the great majority of cases. It must be remembered that, as in other diseases, several of the characteristic symptoms may be absent in a particular case. The chronic cases have the same early course as the acute cases.

While it seems undesirable to attempt to classify the disease too closely and to assign symptoms to the various classes, it is necessary to call especial attention to the fulminating and septicemic type and to the indefinite symptoms of the disease in infants.

The fulminating type is characterized by an onset of overwhelming abruptness and severity. It may be ushered in by a convulsion or by a chill, violent headache, vomiting and fever. Unconsciousness may develop immediately, or brief delirium may precede. Retention of urine usually occurs. A purpuric rash often appears. Stiffness of the neck and other signs of meningitis are usually lacking. The respiration is rapid and difficult, the Cheyne-Stokes rhythm may be present. The pulse is rapid and of poor quality. Death may take place within a few hours. Indeed, the patient may be found dead in bed, having retired in apparently good health. The medicolegal importance of such cases has been pointed out by Netter[88] and should not be overlooked. From the evidence at hand it seems that there are two types of cases with this sudden termination, one in which death is due to sepsis—the meninges not being involved. Such cases are reported by Andrewes,[89] Netter,[88] Herrick[77] and others, and they have come under our observation in a few instances. In the other, a purulent meningitis develops within a few hours, and death is evidently due to the severity of the pathologic process rather than to the sepsis. Indeed, blood cultures are rarely positive in this type of case, which has been in our experience more common than the preceding type.

In the septicemic type in which meningitis develops ,the onset is usually slower and less severe, and a longer time than usual intervenes between the onset and the appearance of the meningeal symptoms. A hemorrhagic rash is almost constant. In a few instances a meningitis may fail to develop, and the disease may continue as a true meningococcus sepsis. This type of case is described fully by Netter,[91] Herrick,[69] Morgan,[90] and others.

Children under a year old constitute the most difficult cases of epidemic meningitis with which we have to deal. In the first place, the diagnosis is very difficult. Not only are we unable to elicit the patient's own sensations, but the objective symptoms are usually atypical and the most characteristic symptoms, stiffness of the neck and Kernig's sign, are so slight as to leave one doubtful of their presence. Moreover, the child is irritable and resists all handling, so that it is practically impossible to tell whether one is encountering an active resistance or a resistance due to a real hypertonicity of the muscles. The stiffness of the neck is best elicited by either holding the child on its side or laying it on a flat table. In this way a tendency for the head to fall back is most readily brought out and observed. The Brudzinski sign is of some value, more perhaps than the Kernig, but it is not so reliable as it is in older children.

The reflexes are very unreliable. Convulsions are present in rather a large percentage of cases, but convulsions occur in so many conditions in children of this age as to be of little diagnostic value. A rash, either hemorrhagic or herpetic, is unusual in young babies. The onset is gradual in a large percentage of cases so far as can be learned from the history. Heiman and Feldstein state that in the majority of their cases the onset is sudden, but Netter and Debré comment on the insidiousness of the onset as being the rule in contradistinction to the abrupt onset in adults and older children.

Netter and Debré mention irregularity of the pulse and respiration as being signs of value. It has not been our experience that in cases of epidemic meningitis the pulse as a rule is irregular. Of course, sinus arrhythmia is well marked in children of this age. According to Holt regular rhythmic respirations are not established until the end of the second year. Therefore, we have not been able to attach much importance to irregular respiration in infants.

There is usually gastro-intestinal disturbance of some sort—greenish slimy stools more frequently perhaps than vomiting, though vomiting is often present. This condition serves to cloud the diagnosis as it may seem that all the symptoms are referable to it.

The best diagnostic points are the bulging fontanelle, the hyperesthesia and the tendency of the head to fall back. Fever is usually present also. A distention of the veins of the head is often associated with increased intracranial pressure. While increased pressure is almost always associated with a bulging fontanelle, we have seen a few cases in which a large amount of spinal fluid was obtained although the fontanelle did not bulge. According to Hutinel and Voisin, tetany may be the only clinical manifestation.

In view of the difficulties of diagnosis, one can do no better than follow the advice of Debré—"In times of epidemic think of meningitis and do a lumbar puncture on every infant sick without apparent cause." We might add that this advice should apply equally when an epidemic is not prevailing.

Not only is the diagnosis difficult in the case of young infants but the prognosis is very grave. Before the use of serum the mortality ranged, according to Flexner, from 90 to 100 per cent. Holt states that out of 24 cases at the Babies' Hospital 23 children died. This high mortality has been greatly reduced by serum therapy, but it has by no means reached the gratifying figure obtained in older children. Heiman and Feldstein give a mortality of 64.2 per cent. in 14 cases. Netter and Debré have a total mortality of 61 per cent. in 18 cases. Correcting this by omitting cases moribund when seen or suffering from some serious complication, they obtain a mortality of 46 per cent. Dopter gives a mortality of 48.6 per cent. The number of cases is not stated. Flexner reports on the case histories of 125 infants among whom the mortality was 49.6 per cent. In our own series of 102 cases under one year of age the mortality has been 44 per cent.

TABLE 9.—SYMPTOMS OCCURRING IN 500 CASES OF EPIDEMIC MENINGITIS

Years of age	Under 1	1 to 2	2 to 5	5 to 10	10 to 20	20
Number of cases	101	42	91	104	84	78
Headache:						
Present	...	8	50	72	73	66
Absent	...	7	5	8	2	1
No information	...	22	21	17	7	1
?	101	5	15	7	2	
Vomiting:						
Present	67	37	76	84	68	53
Absent	22	5	5	6	7	9
No information	12	0	10	14	9	16
Pyrexia:						
Normal or subnormal	5	1	1	3	3	5
Below 100	3	2	10	5	7	6
100 to 103	46	16	41	51	38	37
103 to 105	37	18	24	38	24	21
Above 105	4	4	7	7	5	3
No information	6	1	8	3	7	6
Cerebration:						
Normal	21	5	19	23	28	28
Irritability	43	16	37	32	13	13
Stupor	13	16	25	24	13	14
Delirium	6	4	9	21	24	16
No information	8	1	1	4	6	7
Neck rigidity:						
Normal	8	2	0	4	3	3
Slight increase	56	17	40	45	27	40
Moderate increase	16	19	28	31	30	18
Marked increase	1	1	8	9	9	6
No information	20	3	15	15	15	11
Pupils:						
Normal as to size and reaction	56	16	47	50	17	31
Dilated	6	3	6	13	6	4
Contracted	5	1	3	3	10	5
Sluggish or absent reaction	10	3	8	12	11	7
Strabismus	6	7	3	3	3	4
Unequal	3	1	4	2	7	4
No information	15	11	20	21	20	28
Pulse rate:						
Normal	0	0	0	0	0:30	2:27
Below 100: Regular	7:45	5:18	7:28	18:39	22: 7	32: 5
100 to 120:Irregular	6: 8	9: 5	16:15	24·13	15: 3	12: 3
Over 120: Rapid	53: 5	8: 1	37: 5	24: 1	9	4
No information	35	20	31	38	38	28
Kernig:						
Present	58	29	75	79	63	58
Absent	6	4	3	2	5	5
No information	24	8	13	22	15	14
Indefinite	13	1	0	1	1	1
Macewen or bulging fontanelle:						
Present	85	33	69	73	46	27
Absent	4	2	1	4	3	10
No information	11	7	21	26	31	34
Indefinite	1	0	0	1	4	7
Rash:						
Absent	39	14	21	19	17	23
Present but not described	4	3	5	3	5	0
Macular	1	1	1	4	1	3
Purpuric	0	0	3	0	0	1
Petechial	2	2	12	11	5	5
Erythematous	0	0	1	1	1	0
Herpes:						
Present	0	2	7	12	18	10
Absent	17	5	18	27	13	9
Convulsions:						
Present	36	15	19	14	28	2
Onset:						
Sudden	75	33	74	82	66	55
Slow	13	5	8	2	5	4
No information	13	4	9	20	13	19

Some of the reasons for the high mortality in infants may be considered. One cause is the frequency with which pneumonia occurs in connection with the meningitis. This has happened in six of our fatal cases. Another and more important factor is the tendency of children of this age to develop a basilar meningitis. In 11 of our fatal cases this has happened.

Certain cases of epidemic meningitis in infants run a very chronic course with profound disturbances of nutrition. Such cases are relatively few since the institution of serum therapy but they occasionally occur when, for some reason, the treatment is delayed until late.

Table 9 gives the distribution of symptoms as observed in 500 cases.

Diagnosis, Course and Prognosis.—From our experience in clearing up cases diagnosed as epidemic meningitis by careful clinical study and lumbar puncture, it would seem that the diagnosis, to quote from Wells, is "set about with prowling pitfalls." Aside from the cases of meningism, other forms of meningitis, poliomyelitis and epidemic encephalitis, presenting several well-marked symptoms of meningitis, we have been called to see malignant endocarditis, measles and typhus on account of the rash, hysteria, tetany, typhoid and osteomyelitis on account of the rigidity of the neck, syphilis of the brain and cerebral endarteritis on account of the mental condition, and tetanus and various toxic conditions on account of the convulsions. Cases of epidemic meningitis wrongly diagnosed as some other disease, we did not see, of course, except as we were called to see them late when there had been incorrect earlier diagnosis. Indeed, the diseases from which epidemic meningitis must be differentiated, especially early in the course, are numerous, and its differential diagnosis from certain other meningeal conditions is difficult. The onset of so many diseases comes with headache, vomiting and fever that in the first few hours in a case of ordinary severity we might be dealing with almost any severe infection. It may be well to divide the diseases from which it must be differentiated into two groups, first, systemic diseases in which there is no true inflammation of the meninges but in which there may be well-marked meningeal symptoms such as pneumonia, exanthemata, etc., and, secondly, diseases in which the meninges are really inflamed as in other forms of meningitis, especially the purulent meningitides poliomyelitis, epidemic encephalitis, etc. The diseases of the first group present difficulties of diagnosis from two points of view, first, very early, from their method of onset and constitutional symptoms; secondly, because during their course meningism often develops and makes the differential diagnosis from meningitis practically impossible except by lumbar puncture. A brief discussion of meningism may be of interest. This has been given in part in earlier studies by Du Bois and Neal.[92]

By meningism we mean that condition in which meningeal symptoms arise in the course of some disease, the cerebrospinal fluid being increased in amount but with rare exceptions normal in character. Some difference of opinion exists as to the use of the term. It was introduced by Dupré,[93] who considered it a functional disturbance. Other writers have used the term serous meningitis, pseudomeningitis, meningitis sine meningitide and meningitis infectiosa circumscripta or circumscribed meningitis. This latter term is considered preferable by Plaut, Rehm and Schottmüller.[94] Holt[95] describes a case which showed at necropsy a circumscribed meningitis. Huber[96] in an article on "Pneumococcus Meningitis and Meningism" inclines to the opinion that the pathologic basis is a localized inflammation usually of infectious origin.

In the face of this evidence we cannot deny that cases exist in which the clinical picture and the increased fluid are due to a circumscribed infection, but from our experience it seems quite impossible that this is often the case. We had seen up to 1917, 265 cases in which the outcome was death in 73 cases, recovery in 116 and unknown in 16 cases. Since that time many other cases have been seen, but they have shown nothing in addition to or in contradiction of the data already studied. The diseases which the meningism accompanied are as follows:

Pneumonia	104
Gastro-intestinal disease	27
Scarlet fever (one patient had pneumonia also)	11
Whooping-cough (two patients had pneumonia also)	8
Typhus	4
Otitis media (one complicated with pneumonia; one complicated with mastoid)	7
Erysipelas	5
Tetany	4
Nephritis	4
Measles	3
Influenza	2
Retropharyngeal abscess	2
Trichinosis	2
Concussion of brain	2
Spastic paraplegia	2
Diphtheria	3
Neuritis (one with bronchopneumonia, also)	2
Chicken-pox	2
Neurasthenia	2
Typhoid complicated by pneumonia	6
Orbital abscess	1
Epilepsy	1
Rachitis	1
Streptococcus osteomyelitis	1
Staphylococcus septicemia	1
Heat prostration	1
Endocarditis (one with cerebral embolism)	4
Cerebral thrombosis or hemorrhage	1
Sepsis	1
Tuberculosis (two of spine)	5
Miscellaneous	21
Diagnosis not made	26

Although the patients were seen once in most instances, the progress was carefully followed through the physician in charge.

The meningeal symptoms did not progress. Otherwise we would have done a second puncture. In a few instances a second puncture was made, the fluid remaining normal, however.

In the case of streptococcus osteomyelitis, the necropsy revealed normal brain and meninges. In all fatal cases the severity of the accompanying disease or diseases was quite sufficient to account for death. Of course, this by no means proves the absence of a localized meningeal infection.

We have seen two cases of generalized meningitis following a meningism. One was a case with extensive burns. The first fluid was entirely negative. The second taken four days later yielded a culture of streptococcus hemolyticus. The other was a case of staphylococcus meningitis developing about two weeks after two punctures has been done for the relief of meningeal symptoms due to meningism during a pneumonia.

Weed, Wegeforth and Ayer[97] and Wegeforth and Latham[98] have indicated that lumbar puncture during a septicemia may have some influence in determining the development of a meningitis. Of course in any form of septicemia there is the possibility of a meningitis developing, and the possibility becomes a rather strong probability when there is a meningococcus septicemia. In view of our own experience with lumbar puncture in cases of meningism, many of which were at stages of a pneumonia at which a septicemia must have been present, it seems to us that the danger of lumbar puncture resulting in the development of a meningitis must be very slight. Certainly it is not so great as the danger of neglecting a lumbar puncture in the presence of meningeal symptoms. And it may safely be assumed that few physicians will undertake the operation unless meningeal symptoms are present.

Of course, the amount of fluid depends on the stage at which the puncture is done. We have withdrawn very large quantities—from 80 to 100 c.c. In other cases the fluid has been but little increased above normal. It is commonly accepted that in true meningitis the fluid is inflammatory in character—of the nature of an exudate. Such a fluid shows an increase in albumin and globulin and in the number of cells. On the other hand, in a meningism, as we use the term, the fluid is of the nature of a transudate. According to Anglada[76] the albumin present in normal spinal fluid is serum globulin while in meningitis it is serum albumin. Except in a few cases the cells have not been increased, neither has the albumin and globulin content, and Fehling's has been readily reduced. In all cases the fluids have been negative bacteriologically, by smear, culture and animal inoculation. In a few cases of meningism there have been some changes in the cytology or chemistry or both. These have occurred for the most part in three groups, first, with severe and prolonged convulsions—notably the convulsive type of whooping-cough, secondly, cases of long duration especially in patients about to die, thirdly, where there is an inflammation near the dura as in otitis media or sinusitis. These changes are doubtless due to minute hemorrhages or to congestion. In two cases of typhus there were pathologic changes, in one an increase of cells, 95 per cent. mononuclears and in the second, an increase in the albumin and globulin and also in the cells—100 per cent. mononuclears. In the third case of typhus, the fluid was bloody, and in the fourth case a puncture was not done. In mumps there are usually changes in the fluid. Kaunitz[99] has described this.

A case of tetanus showed a moderate increase in the albumin and globulin with a normal cytology.

In a case of cerebral embolism with a septic endocarditis there was an increase in the albumin and globulin with a normal cytology. In a case of cerebral thrombosis or embolism there was a slight increase in cells, also in the albumin and globulin.

Of course, tetanus and cerebral embolism or thrombosis do not represent a true meningism. In these cases there is a definite lesion of the central nervous system. A case of spastic paraplegia showed a slight increase in the albumin. In meningism there may occur signs of meningeal irritation as marked as in true meningitis, even loss of knee-jerks, dilatation and rigidity of the pupils, strabismus or ptosis.

Differential Diagnosis.—Pneumonia.—Returning from this digression on meningism to the differential diagnosis of epidemic meningitis from those diseases in which there is no inflammation of the meninges, we should consider pneumonia first. Especially in children with an apical or central pneumonia when the physical signs are late in appearing, the diagnosis is extremely difficult, indeed, quite impossible except by lumbar puncture. Not only is the sudden onset with chills and fever, headache, vomiting, occasionally delirium and often convulsions in children very suggestive of meningitis, but, as may be seen from the table, meningism develops in pneumonia more frequently than in any other disease. These meningeal symptoms, as stated earlier, cannot be diagnosed from a true meningitis with any degree of certainty excpet by a lumbar puncture. Of course, after the physical signs have appeared, one may strongly suspect that the meningeal symptoms are due to a meningism, but it is much safer to do a lumbar puncture and be sure. Not only is the diagnosis cleared up, but the symptoms are greatly relieved if it is a meningism. If the case is an epidemic meningitis with the pneumonia, as occasionally happens, and not a meningism or a pneumococcus meningitis secondary to it, the early institution of treatment is of great advantage.

Gastro-enteritis.—This disease in young children is often accompanied by meningism. Diarrhea, however, is unusual in meningitis except in babies in whom it may appear as greenish slimy stools.

Typhus Fever.—This may offer difficulties in diagnosis. The abrupt onset, the marked meningeal symptoms, intense headache, and the rash are quite characteristic of meningitis. The rash, however, appears later in typhus and passes through various stages before becoming hemorrhagic, and the temperature is not so irregular as it usually is in meningitis. The spinal fluid in typhus showed, in the few instances in which we have examined it, some change from the normal both in chemistry and cytology.

Small-pox.—Before the appearance of the eruption this disease may suggest meningitis. Fortunately, both small-pox and typhus are so rare that they do not ordinarily offer a real problem in the differential diagnosis. They must, however, be borne in mind.

Influenza.—The onset with fever, headache and pain in the back and legs, often sufficient to give stiffness of the neck and a slight Kernig, simulates meningitis. A herpetic eruption often adds to the difficulty of diagnosis. Indeed, the meningeal symptoms may be so pronounced that a lumbar puncture is necessary.

Typhoid Fever.—The onset of typhoid is usually more gradual than in the case of meningitis. The rose spots may suggest the eruption, but they are later in appearing in typhoid. A blood count helps in the differential diagnosis since there is a low white count in typhoid and a moderately high leukocytosis in meningitis. The blood culture early would also be of value and the Widal later.

Tetanus.—This may suggest meningitis in its opisthotonus and hyperesthesia. The fever and constitutional symptoms of the onset of meningitis are lacking in tetanus, however, and the trismus, rigidity of the abdominal wall and characteristic convulsions of tetanus are lacking in meningitis. Very rarely trismus may occur in meningitis. A rash, either herpetic or hemorrhagic, is lacking in tetanus, but it is also often absent in meningitis. The mind is clear in tetanus, but it may be so in meningitis. The history of an injury is of value in diagnosing tetanus. Of course, the convulsions of tetanus may suggest the convulsions of meningitis, but when carefully studied, their characteristics as to mode of onset, course and severity, leave little question as to their real nature.

Measles, Scarlet Fever, Diphtheria, Whooping-cough.—In any of these conditions, meningeal symptoms may arise, but the question in diagnosis is rather to discover whether a meningitis is complicating the disease than to decide between a primary meningitis and the disease present. This must be cleared up by lumbar puncture.

The fulminating forms of meningitis, in which the patient develops coma, early present additional difficulties in diagnosis. Poisoning, diabetic or uremic coma or cerebral hemorrhage may be suspected. The absence of fever in all these conditions will be of help in ruling out meningitis, but it must be remembered that not very infrequently the temperature in meningitis may be normal or subnormal. The history and, in the case of diabetes or uremia, the examination of the urine will be of value. Again, one must remember that a transitory glycosuria may occur in meningitis. Lumbar puncture is so valuable an aid in the diagnosis of such obscure and serious conditions that one cannot afford to omit it.

We will now consider the diseases in which the meninges are really involved.

Other forms of purulent meningitis due to the pneumococcus, streptococcus, influenza bacillus, staphylococcus and colon bacillus, occurring in frequency in this order in our experience, can be diagnosed in no way from epidemic meningitis except by the bacteriologic examination of the spinal fluid. The appearance of the spinal fluid gives no clue to the infecting organism. The history of the case is of doubtful value. While the history of pneumonia, middle-ear disease, an operation on the nose or throat, etc., may make one suspect that the organism causing the meningitis is other than the meningococcus, it by no means follows that this is true, and all cases of purulent meningitis should certainly be given the benefit of anti-meningococcic serum until the diagnosis is established. Of course, a certain number of these forms of meningitis are primary. If a hemorrhagic rash is present, it is more probable that the case is one of epidemic meningitis, but, as has been stated before, the rash occurs in only a small percentage of sporadic cases of epidemic meningitis, and it may occur with septicemia in the other forms.

Tuberculous meningitis ordinarily is easily diagnosed from epidemic meningitis by its gradual onset, low temperature, irregular pulse, drowsiness passing into coma, projectile vomiting occurring rather late, the less marked stiffness of the neck and the less pronounced Kernig. Under two main conditions, would one be puzzled in making the differential diagnosis, first, if a tuberculous meningitis is, contrary to rule, rather sudden in its onset with a temperature of 103 to 104 degrees, as may be the case if it is an unusually acute form. In such cases, the fluid is usually slightly cloudy and shows an excess of polymorphonuclears. Fortunately, with these fluids, the tubercle bacilli are easily found. Secondly, if a case of epidemic meningitis is seen after it has passed into a somewhat chronic condition, the history rendered indefinite by inaccuracies on the part of the relatives or by a series of complications that have masked the underlying condition. A case in point was M. M., 21 months old, seen June 5, 1916, with the history of an abscess on the left side of the neck two months previously, followed by an otitis media on the right side, some pulmonary symptoms (not, however, of a frank pneumonia) and an iritis and hypopion of the right eye, for which she had been sent to the hospital for eye diseases. During a part of this time meningeal symptoms had been present. When seen she had a temperature of 99 degrees, a regular pulse of 140, slight stiffness of the neck, a well-marked Macewen and absent knee-jerks. The left pupil was dilated and did not react to light; the right was contracted, and the tension of the eye-ball was diminished. The child was in a stuporous condition, and there was a history of frequent vomiting for the past few days. This case had much to suggest tuberculous meningitis, both in the history (the breaking down of the gland of the neck and the pulmonary condition) and in the physical signs. The eye condition and the regularity of the pulse made us suspect a possible epidemic meningitis, which it proved to be. This case will be referred to later in discussing the course of epidemic meningitis.

In such cases the diagnosis will rest largely on the examination of the spinal fluid, and this may present some difficulties if the meningococci have cleared up and the fluid becomes practically clear, with the percentage of mononuclears equaling or exceeding the polymorphonuclears. These findings together with a decreased reduction of Fehling's will strongly suggest a tuberculous meningitis. Usually, however, in these chronic conditions a few meningococci will persist in the fluid, and if the case is one of tuberculous meningitis in which the first examination is not conclusive, repeated examinations of the spinal fluid should reveal the tubercle bacilli by smear. At any rate, animal inoculation will do so. The tuberculin reaction is of value, especially in young children.

Syphilitic meningitis in the acute form is rare in children but occurs quite frequently in the secondary stage of acquired syphilis. According to Castaigne and Paisseau,[100] it has a somewhat irregular onset, sometimes gradual sometimes abrupt and very few marked signs of meningitis. The headache is very intense, worse at night and resistant to all treatment except mercury. Fever is absent, and disturbances of the pulse or respiration rarely occur. The Babinski sign is present, especially if there is an accompanying hemiplegia. Paralyses, except of the ocular muscles, are rare, however. The stiffness of the neck and Kernig are much less marked than in epidemic meningitis. Much will depend on the history of the case and the Wassermann, both of the blood and spinal fluid. The Wassermann is ordinarily positive in the spinal fluid in syphilitic meningitis. The spinal fluid is under increased tension and is usually clear, but it may be yellowish or very rarely slightly hazy. The cells are greatly increased with usually a preponderance of lymphocytes. The albumen and globulin are increased, but usually not in proportion to the cells. These spinal-fluid findings, then, will clear up the diagnosis so far as epidemic meningitis is concerned, unless the patient is seen late and one suspects that one may be dealing with a mild epidemic case, that has nearly recovered without treatment. On this point the Wassermann test and the response to mercurial treatment will make the diagnosis.

Poliomyelitis.—Early differential diagnosis between epidemic meningitis and poliomyelitis, either the nonparalytic form or the paralytic form before the paralysis has developed, is very difficult clinically. In poliomyelitis the onset is usually abrupt, with fever. Quite occasionally there is a history of an anginal or a gastro-intestinal attack, especially the latter, preceding the true onset by three to four days. Rarely the onset is insidious. The temperature is usually higher at the onset and of shorter duration than in epidemic meningitis. Prognosis in cases showing a rapid pulse and respiration is serious. Delirium is rare in poliomyelitis. Drowsiness alternating with irritability is the rule. In some cases this drowsiness goes on to stupor which lasts for two or three weeks, strongly simulating the picture of tuberculous meningitis. Convulsions may be severe and prolonged in the higher type of the disease. The reflexes are often increased early. Later they are diminished or lost. In the spinal type they are frequently unequal. This is often a helpful point in differentiating the case from one of meningitis, in which the reflexes usually show the same changes on both sides.

The pupils as a rule are equal and react to light. There may be nystagmus, strabismus, or ptosis. Vomiting is frequently an early sign. Diarrhea occurs more often than constipation. Very rarely, in severe cases there may be retention or even suppression of urine. Hyperesthesia is almost always present. Paralysis or paresis occurs in a large percentage of cases, but it is absent in many cases of poliomyelitis, and it may occur in epidemic meningitis. The presence of a rash will point to the latter condition. The spinal fluid usually determines the diagnosis, as in most instances it is clear, contains an excess of mononuclears, a slight to moderate increase in the albumin and globulin and has a normal reduction of Fehling's. It yields no growth on media. In some few cases, however, the fluid is slightly turbid and contains an excess of polymorphonuclears. In these cases it is difficult to be sure that one is not dealing with a mild case of epidemic meningitis, in which the organisms have not yet appeared in the spinal fluid, and the diagnosis must wait on the progress of the case.

Epidemic or Lethargic Encephalitis.—This does not usually offer much difficulty in diagnosis because of the slow onset, low temperature, extreme lethargy, asthenia, diplopia and other cranial-nerve palsies which are found in the more typical cases. On the other hand, many cases show extreme restlessness, rather than asthenia, and insomnia rather than lethargy and somnolence. Some cases, moreover, have an acute onset and strongly suggest epidemic meningitis. I have seen a few cases diagnosed as epidemic meningitis that proved to be encephalitis and an occasional case diagnosed as encephalitis that proved to be epidemic meningitis. Indeed, epidemic encephalitis is so protean in its manifestations that it may simulate almost any involvement of the central nervous system. Some of these manifestations as catatonia; marked tremors; spasticity; twitchings of localized groups of muscles; temporary blindness; inability or refusal to speak, lasting a short time; meaningless screaming; occasional periods of delirium lasting a few minutes; disturbances of sensation; excruciating pains in the limbs, evidently of posterior nerve-root origin, do not in any way suggest meningitis. On the other hand, retention of urine, failure of the pupils to react to light (though the pupils are more often unequal in encephalitis than in meningitis), intense headache and vomiting—any or all of which may occur in encephalitis, are found also in cases of meningitis.

The diagnosis may be cleared up by lumbar puncture. In epidemic encephalitis the fluid is very similar to that in poliomyelitis. It is practically always increased in amount and with rare exceptions shows changes in the cytology or chemistry or both at some stage of the disease. The fluid is usually clear but in rare instances it may be slightly hazy or slightly hemorrhagic, a fibrin web occasionally being seen. In rare instances of cases that seem unquestionably encephalitis the fluid may be normal. The cells are usually increased from slightly above normal to 1500, in our experience. As a rule the cell count is rather lower in epidemic encephalitis than in poliomyelitis, but there are many exceptions to this. In a very large percentage of cases the mononuclears predominate, but as in poliomyelitis, polymorphonuclears occasionally are in excess. The albumin and globulin are slightly to greatly increased. The increase in cells and protein content is not necessarily in the same ratio. The glucose present, as shown by the reduction of Fehling's, is not diminished (unless it is masked by a large amount of protein)—indeed some workers, among them Foster,[101] have stated that it is sometimes increased above normal. This is also true in poliomyelitis, as was shown by work done in the Meningitis Division[79] of the Research Laboratory in 1916. The colloidal gold curve evidently follows the protein elements present and is apparently not diagnostic.

Meningeal Hemorrhages.—These are rather rare, and they seem to have been studied more extensively by the French than by other writers. According to Klippel,[102] the causes may be divided into obstetric, surgical or traumatic and medical. Under medical causes may be mentioned cerebral tumor, alcoholism, arteriosclerosis, atheroma of the vessels, nephritis, diseases of the heart, and certain infectious diseases, such as syphilis, small-pox, tuberculosis, icterus gravis, septicemia, scarlet fever, etc. The onset is usually very sudden, and the patient rapidly becomes unconscious. There are well-marked meningeal symptoms, but the temperature is ordinarily not elevated. The picture is very like that of a severe case of epidemic meningitis, but lumbar puncture reveals a bloody fluid that is of uniform intensity when collected in successive test tubes, thus distinguishing it from a bloody fluid due to the accidental puncture of a vein which clears as the fluid is withdrawn. A careful bacteriologic examination of the fluid must be made as hemorrhagic fluids also occur in the purulent meningitides.

Aseptic Meningitis.—It must be borne in mind that the intraspinal administration of serum is usually followed by a meningeal reaction with a cloudy fluid, increased in amount. This fluid is, of course, sterile but otherwise it is very much like the fluid of a true meningitis, showing a marked increase in albumin, gobulin and cells with a preponderance of polymorphonuclears. This will occur when serum is injected intraspinally in tetanus poliomyelitis, tuberculous meningitis or meningism. Therefore, this marked modification of the fluid must be kept in mind, when a cloudy fluid is obtained after a previous intraspinal serum injection.

Meningitis Sympathetica.—This is a term applied to the meningeal condition often found when an active inflammation, such as an otitis media, sinusitis or brain abscess exists in the vicinity of the meninges without actually invading them with the infecting organism. This has been described by Strauss.[103]

Well-marked signs of a meningitis are seen, and the spinal fluid shows changes probably due to a sympathetic reaction of the meninges to the contiguous inflammation. These changes consist in an increase in the amount of fluid which is often hazy, an increase in cells with polymorphonuclears often predominating, an increase in the albumin and globulin and a normal reduction of Fehling's. There are no organisms by smear or culture. Of course, if the adjacent inflammation extends, the meninges may later become involved in a true purulent meningitis.

The differential diagnosis is made by the discovery of the underlying cause and the examination of the spinal fluid. Here again it is necessary to remember that an otitis media, for instance, and an epidemic meningitis may exist side by side, quite independently of each other.

Course.—The course of epidemic meningitis is varied and it is difficult to generalize in regard to it. Some idea may best be gained by following the outline of the clinical types. Cases of the septicemic type, that is, in which there may be no meningitis, the septicemia dominating the clinical picture, are rare except in certain outbreaks. It is probable, however, that there is a more or less transient septicemia or bacteremia in all cases of epidemic meningitis with a hemorrhagic eruption. We have studied but two or three cases of the true septicemic type, one of which was as follows:

M. D., three years old, suddenly developed on Oct. 30, 1917, a high fever, extensive purpuric rash and swelling of the joints of both wrists and the left thumb. A slight strabismus followed. It was thought to be a case of purpura. A blood culture was done November 3, which yielded the meningococcus. Although there were practically no meningeal symptoms except the strabismus, a lumbar puncture was done. The fluid was bloody, but fearing that the blood might be concealing a cloudiness, antimeningitis serum was given. Shock promptly developed. Since the fluid was sterile and the development of shock made us unwilling to risk repeating the serum unless it was absolutely necessary, no further treatment was given. The child ran an irregular septic temperature during November. The rash faded, and nephritis developed. There were no well-defined signs of meningitis, however. Finally, on November 24 a second puncture was done, and 30 c.c. of slightly cloudy fluid withdrawn. The fluid was typical of that in convalescing meningitis. The culture yielded no growth, and there was a slight increase in the albumin and globulin, a good reduction of Fehling's, and a moderate increase in cells. No serum was given, and the patient seemed somewhat improved after the puncture. Later, she became worse, and on December 1 a third puncture was done, and 30 c.c. of distinctly cloudy fluid were withdrawn. As the fluid had increased in cloudiness, 20 c.c. of serum were cautiously given, and again there was a very severe and immediate reaction. One colony of meningococcus grew from this fluid, and the chemical and cytologic findings were in line with the presence of an acute meningitis. No more serum was given, but an autogenous vaccin was prepared and administered. The temperature became normal within a week and remained so. The child made a perfect recovery.

The fulminating type runs a rapidly fatal course, and death takes place in from two hours to two or three days. The pulse in these cases is often so weak as to be almost imperceptible, and Maclagen and Cooke[66] sometimes found hemorrhage of the adrenals on necropsy of these cases. The fluid may be nearly clear with practically no cellular reaction or it may be extremely purulent. Sometimes there seems to be some response to serum treatment and stimulation, but it is brief. The temperature may be normal or sub-normal. One patient that we recently saw showed some improvement after the serum which he received four times (twice in the first 24 hours of his illness), and stimulation with adrenalin and atropin. A hemorrhagic fluid was obtained, however on the fourth puncture, and he died about 20 hours later, having been ill three and a half days. Throughout the time he was delirious or unconscious except for brief periods of lucidity. Death may occur in this form in a few hours. The patient is suddenly struck down while in apparently excellent health, and coma develops in a few minutes from which he does not arouse. Hence, epidemic meningitis should be considered as a possibility in instances of sudden death.

In the ordinary acute form in which the patient is either well on the road to recovery or has died within 10 days or two weeks, the course is naturally more varied. In such instances the response to serum may be very prompt, and after a single dose there may be, as the husband of such a patient once said to us, "all the difference between night and day." In this case the patient was seen about 24 hours after she became ill and was at the time wildly delirious, crying out with headache. She vomited repeatedly and had a temperature of 103 degrees. The next morning she was rational and fairly comfortable. The vomiting had stopped, and the temperature had fallen to 100°. Her recovery was rapid and uneventful. In most cases, however, the progress is slower, and the patient shows a gradual improvement, 5 to 10 days elapsing before he is comfortable and has a normal temperature. The proportion of fatal cases occurring at this period is not large. Perhaps about 20 per cent. of the patients in fatal cases die between the third or fourth and tenth days of the disease. There is usually nothing especially striking about the course of the fatal cases occurring at this period. The patients simply do not respond clinically to treatment, and the organism persists in the spinal fluid, or death may be due to some complication especially pneumonia.

In considering the course in the chronic forms, we will first take up the types in which a basic meningitis develops with a walling off of the ventricles and resulting dry taps. While this form may develop in patients of all ages, even in adults, it occurs with by far the greatest frequency in children under a year of age. It may develop early after only one or two treatments, or the patient may at first show a good deal of improvement so that one has begun to expect a favorable outcome. The development of the basilar condition usually manifests itself not only by a dry tap (in these cases the serum will not run into the spinal canal as it will in cases in which the dry tap is evidently due to a diminished quantity of spinal fluid) but also by a rise in temperature and an accentuation of the meningeal symptoms, a greater bulging of the fontanelle, more spasticity, a greater retraction of the neck, etc. Death may occur a few days after this condition develops, or the disease may run on for many weeks, the child becoming more and more emaciated and the opisthotonus more and more marked. Sometimes the child becomes both deaf and blind before death finally ensues. In one case of this type the adhesions at the base of the brain finally gave way, and it was possible toward the end to withdraw nearly clear spinal fluid in which the meningococci still persisted. The results of ventricular puncture are discussed under treatment.

The Relapsing Type.—In 1 to 2 per cent. of treated cases, one or more relapses occur. Ker[104] considers that in cases wihout serum treatment the percentage of relapses is as high as from 15 to 20 per cent. The spinal fluid becomes sterile, the patient responds well to treatment and seems to be making good progress. After an interval varying from a few days to a week or two, however, there is a return of the symptoms, and lumbar puncture reveals a fluid of increased cloudiness in which the meningococci are again present. In our experience the relapse has always occurred within a short period, less than two weeks, from the time when treatment for the original attack was stopped. According to Netter and Debré,[2] a relapse may take place after three or four months, and an Australian army surgeon told me of relapses occurring after even longer intervals. In the case of these long intervals the question arises as to whether we should designate the illness as a relapse or a second infection. In one instance in our experience two relapses occurred. In general, the patients have recovered from the relapses, though we have not seen enough such cases to make the statistics of any value. It may be of interest to note that one of our patients who survived a very severe attack of meningitis, died of a second attack that occurred three or four years later. The chronic form in which there is no development of basilar meningitis is not unusual. We may consider this form in two divisions, first, the course in fatal cases and, secondly, the course in cases that recover. In cases in which death occurs, the course varies considerably. In certain instances the fluid continues to show a positive culture at nearly every puncture, and the patient though he improves slightly from time to time, especially early in the treatment, grows progressively worse until death occurs after 15 or more punctures have been done. In other cases periods occur in which the symptoms show marked remission for several days and the spinal fluid may from time to time be sterile so that one believes that convalescence is beginning, only to be disappointed by a sharp exacerbation of symptoms. This temporary improvement, which does not go so far as to lead one to designate the exacerbation as a relapse, may be repeated several times during the course of the disease. At times these exacerbations are sudden and very sharp. As one mother described it to me: "At noon she had a headache, she vomited, and then she couldn't hear." Occasionally we see cases in which the fluid becomes sterile after the first few punctures but continues to show a considerable increase in the albumin, globulin and cells and a poor reduction of Fehling's, the latter being a finding which is usually associated with a poor prognosis. These cases show improvement, and yet from time to time there are exacerbations that lead one to fear that the inflammation is progressing though the organisms are shut off from entering into the spinal fluid. Such a case was as follows:

L. B., four years old, taken ill May 16 and first seen May 20, with typical signs of meningitis. On the twenty-first deafness developed. The condition improved, and the spinal fluid became sterile with a good reduction of Fehling's after three injections but later showed organisms again. After the eighth injection it became sterile and remained so during the last nine punctures, though in the subsequent punctures the reduction of Fehling's was poor or lacking. The child seemed for some time to be doing very well, but there were slight exacerbations every 5 to 10 days. She would complain of headache. There occurred some rise in temperature and vomiting usually, however, after some illadvised article of food. These symptoms would quiet down after lumbar puncture. During the intervals, which became gradually longer, the child seemed very comfortable, was not emaciated, ate and slept well and played with her toys on the bed. Finally, during the night of July 4 she was seized with violent vomiting and diarrhea that left her completely prostrated with a very poor pulse, comatose and apparently unable to see when aroused. The vomiting yielded to atropin and the condition of the pulse improved, but very severe and distressing convulsions developed in a day or two, and death followed about July 10. It seems quite probable that a brain abscess had developed. In one case, S. K., six years old, the fluid cleared up both as to bacteriology and chemistry, but the patient continued to grow weaker and finally died. It was shown at necropsy that an abscess had formed.

In this case, however, there were focal symptoms, in spasticity on the opposite side from the abscess, and there were none of the symptoms of a violent exacerbation that occurred in the previous case. Certain other prolonged cases clear up so far as the meningitis is concerned, judging both by the clinical signs and the fluid but die of some complication. Thus, one patient died of a decompensated heart during convalescence. Another, cardionephritic and alcoholic apparently overcame the meningitis but died two weeks later probably from the cardiac condition. Several have died of pneumonia, the meningitis having apparently cleared up. Most of these chronic cases run an irregular but not a very high temperature. The pulse is usually rapid, over 100. There is marked emaciation. A low muttering delirium occurs at times, and a considerable dulling of the mentality. Late there is usually loss of sphincter control. Contractures of the legs ordinarily develop toward the end, but the opisthotonus that characterizes the basilar condition rarely occurs.

Fortunately, the outcome in the chronic forms is frequently favorable. It is often very difficult, however, to persuade the family to allow us to continue with the treatment which is somewhat painful and apparently not productive of results, and one has need of all one's patience and courage in dealing with the situation. The following is a fairly typical case:

W. R., aged 13, seen July 26, had been taken sick July 24; the symptoms were characteristic; there was herpes on the lips, and the patient was delirious. Fifty cubic centimeters of cloudy fluid were withdrawn, showing meningococci by smear and culture; Fehling's solution was not reduced; 20 c.c. of serum were given. Lumbar punctures were done daily until August 6 except July 30, August 3 and August 5, when improvement clinically and in the fluid had seemed to warrant their omission. At no time, however, had the temperature been normal or the patient's general condition very encouraging. August 6, the patient suffered considerably from shock at the time of puncture, and no more punctures were attempted until the twelfth, as the family strongly objected. At this time the patient was greatly emaciated: The head was retracted and swallowing was almost impossible; the temperature was 104 degrees; 50 c.c. of turbid fluid were withdrawn and 10 c.c. of serum injected without untoward symptoms. A small quantity was given on account of the shock at the previous injection. This fluid showed meningococci by smear and culture and no reduction of Fehling's solution; punctures were repeated August 13, 14, 15, 16, 17, 19 and 21, no serum being given at the last puncture. Seventeen punctures were done. There were no organisms after August 15, and there was a good reduction of Fehling's solution after the sixteenth. An autogenous vaccin was given subcutaneously August 13, 17 and 21, in doses of 250, 500 and 750 million. The patient made a satisfactory recovery.

In several other instances we have found it necessary to do a larger number of punctures than this. Twenty were necessary in one adult who had a relapse and was desperately sick in both attacks, being delirious practically all the time and becoming greatly emaciated. Curiously enough, he ran a practically afebrile course except for a day or two at the beginning of the attack and also at the beginning of the relapse. Vaccin was used in this case also. In another case 28 punctures were necessary though the patient did not seem alarmingly ill at any time, being rational except for occasional delirium at night, and developing practically no retraction of the neck. In spite of taking his food well he became greatly emaciated. His pulse was good throughout and he had very little temperature after the first few days of treatment except during his serum reaction. The serum treatment was supplemented by vaccin.

A case of rather unusual interest was that of a child, 21 months old, previously referred to under the differential diagnosis of epidemic and tuberculous meningitis. It is as follows:

M. M. seen June 5, had been ill for two months, and it was difficult to estimate when the meningitis had begun. She was greatly emaciated and presented the clinical picture of an advanced case of tuberculous meningitis. The spinal fluid cleared up after seven injections of serum, and the clinical condition improved also. The vomiting stopped and she began taking nourishment better. An eighth puncture for the relief of pressure was done June 30, but no serum was given. Though she was taking nourishment fairly well, it was evident that a profound state of malnutrition existed, and she was sent to a hospital for treatment. She was brought home during August and when seen was still emaciated and had an excessive growth of hair on the extensor surfaces of the arms and legs and on the back. Soon after this she began to improve in nutrition, gained in weight and strength, and the hairiness disappeared. She began to walk and talk again and when seen the following January seemed entirely normal except for the blindness of the right eye.

We have noticed this excessive growth of hair in another case in which there was profound malnutrition with the history of an acute meningitis some months previously. This too disappeared as the nutrition improved. The only reference we have seen to this rather unusual phenomenon is in Netter and Debré.[2] As to the cause we have no idea unless we fall in line with the present tendency and ascribe it to some maladjustment of the internal secretions.

The course of the disease is greatly modified by the serum treatment. From the descriptions before serum was used, one gets the impression that cases lasted three months quite frequently and that they sometimes ran on from four to six months. While a few of our cases, especially those that were untreated for a long time, have died at the end of about three months, the duration of the chronic cases is usually one to two months. Ker[104] reports a case of recovery at the end of 105 days, and Holt[95] reports one patient recovering at the end of 84 days and another at the end of 102 days. According to Holt, the usual duration of untreated cases was from three to six weeks, while in 220 cases receiving serum the average duration of active symptoms after the first injection was 11 days. This would probably be, on an average, four to five days after the onset of the disease. It is reasonable to believe, therefore, that many of the cases that without serum treatment possessed sufficient resistance to survive so long and even to recover after months of illness with the help of serum would have made a fairly rapid recovery.

Prognosis.—The mortality figures of epidemic meningitis have been just about reversed since the introduction of anti-meningitis serum. While previously 70 to 80 per cent. died and 20 to 30 per cent. recovered, now we can count on only 20 to 25 per cent. of deaths and 75 to 80 per cent. of recoveries. While the exact mortality before serum treatment was instituted is sometimes questioned, in certain comparatively recent epidemics it has been fairly well established. In New York in 1905, out of 1780 cases there was a mortality of 76 per cent. The mortality in Belfast was over 70 per cent. before serum was used, and it was reduced by Robb to[105] 30 per cent. by the serum. In cases occurring simultaneously but not treated by serum the mortality remained over 70 per cent., showing that the severity of the epidemic had not decreased. In Edinburgh, according to Ker, the death-rate before the serum was used was over 80 per cent.

Perhaps four factors may be considered as influencing the prognosis, first, whether the cases are sporadic or epidemic and if epidemic the time of the epidemic at which they occur; secondly, the age of the patient; third, the presence of certain unfavorable symptoms; fourth, the time at which serum is administered. In general, sporadic cases are considered to be less severe than cases during an epidemic especially during the early part of it. It should be noted, however, that sporadic cases are usually not diagnosed as promptly as cases occurring during an epidemic. It is generally accepted that during the latter part of an epidemic cases are less severe than at the beginning. In spite of the fact that one may feel reasonably sure that out of a hundred properly treated cases recovery will take place in from 75 to 80, the prognosis of an individual case is exceedingly difficult. Patients that are seemingly desperately ill when first seen often respond with surprising speed to serum treatment, while others apparently not nearly so grave will show some temporary improvement, so that one is inclined to give an encouraging prognosis, then lapse into a chronic condition and die. As I have already pointed out, however, many cases with a tedious course end in recovery. The age of the patient has a very definite bearing on the prognosis. With children under a year old we have not been able to maintain a lower mortality than about 45 per cent. This is, however, a great improvement over the mortality before the use of serum when it was practically 100 per cent. Cases with the fulminating type of onset are very serious, and certain symptoms are generally regarded as indicating a poor prognosis. Netter and Debré give the following: Loss of consciousness, violent delirium, complete insomnia or profound stupor, an adynamic state, convulsions (especially in older children and adults), carphology, generalized trembling, purpuric eruption. Of course, much will depend on the length of time any of these symptoms persist. The prognosis is not unfavorably affected by a high temperature, marked rigidity of the neck or severe headache. Netter and Debré consider that irregularity of the pulse is of no consequence. Personally, we much prefer the pulse to be regular unless it is evidently a sinus arrythmia though we have never regarded an irregularity with at all the same concern as a rapid pulse of poor quality. One of the most important factors in the prognosis is the date at which serum treatment is instituted.

Table 10 is taken from Heiman and Feldstein[1] (p. 279), compiled from Flexner, Netter, Dopter and Levy.

TABLE 10.—MORTALITY STATISTICS COMPILED BY HEIMAN AND FELDSTEIN

	Levy			Netter			Flexner	Dopter
	Number of cases	Deaths	Percentage of mortality	Number of cases	Deaths	Percentage of mortality	Percentage of mortality	Percentage of mortality
First day	6			44	9	20.9	18.1	8.20
Second day	33	3	9.09					
Third day	37	7	18.91					
Fourth day	24	4	16.66	32	11	33.3	27.2	14.40
Fifth day	14	3	21.43					
Sixth day	11	3	27.27					
Seventh day	9	3	33.33					
After first week	26	7	26.92	23	6	26.0	36.5	24.10

Our mortality statistics by years up to July, 1919 are given below, also the mortality statistics for the first 500 cases, up to the fall of

1919, being classified according to age and time of treatment. Since 1919 the number of cases has been comparatively small and the tables have therefore not been changed.

TABLE 11.—MORTALITY STATISTICS FROM JULY 1, 1910, TO JULY 1, 1917

	Total number cases	Patients recovered	Patients died	Patients not counted in mortality	Mortality percentage
1910–1911	17	10	7	0	41.0
1911–1912	25	7	15	3	60.0
1912–1913	29	17	12	0	41.0
1913–1914	41	30	11	0	26.0
1914–1915	38	25	13	0	34.0
1915–1916	61	39	17	5*	28.0
1916–1917	87	67	18	2*	21.0
1917–1918	114	90	22	2*	19.0
1918–1919	78	62	16	0	20.5

* Not counted in mortality statistics.

The 1911 to 1912 statistics need some explanation. Four cases developed basic meningitis, and in five other fatal cases the patients were either in hospitals already or were sent there where we had little oversight of the treatment.

Of the 17 cases in 1915 to 1916, one patient had a serious heart condition, one in a hospital developed an abscess at the point of the puncture. Laminectomy was advised by us but was not done. The meningeal symptoms had entirely cleared up. Two were fulminating cases. One case developed basic meningitis.

Of the 18 patients dying in 1916 to 1917, one had a serious condition of the heart, two were moribund when seen, and two developed basic meningitis.

TABLE 12.—FIVE HUNDRED CASES—MORTALITY 27 PER CENT.

Cases	Years	Mortality, per cent.
102	under 1	44
47	1 to 2	28
88	2 to 5	16
100	5 to 10	19
84	10 to 20	21
79	over 20	31
500		27

Time between Onset and Treatment, with Mortality

Cases	Time	Mortality, per cent.
200	1 to 3 days	23
137	4 to 7 days	27
63	7 to 14 days	37
47	2 to 3 weeks	47
22	over 3 weeks	40
509		

Our average mortality is high since the number of cases seen the first three years was small. Our mortality ran high at that time doubtless because many cases were seen late and also because we were comparatively inexperienced in treating the disease. For the last three years, however, the mortality has been about 21 per cent., as is shown by the table. This result is fairly satisfactory, when one considers that it includes cases of all degrees of severity, and a large number of infants under one year of age, among whom the mortality is always high.

Complications and Sequelæ.—Not only is epidemic meningitis a serious disease as regards life, for even with serum treatment the mortality averages higher than in most infectious diseases, but the complications and sequellæ, though greatly reduced in number by serum treatment, are nevertheless perhaps more numerous and serious than in any other acute infection with the exception of poliomyelitis and epidemic encephalitis. As many of the complications remain permanently and become transformed into true sequelæ no effort will be made to distinguish exactly between them. In general perhaps it will be convenient to describe them under two heads:

1. Infectious complications not relating to the central nervous system.
2. Complications involving the central nervous system.

1. Infections Not Relating to the Central Nervous System.—*Respiratory.*—Pneumonia is one of the most frequent complications, strictly speaking. It is not infrequently the cause of death when the meningeal symptoms seem to be improving satisfactorily. The pneumonia is usually due to the pneumococcus. Bronchopneumonia also occurs. Pleurisy either fibrinous or purulent is far rarer.

Cardio-vascular.—Pericarditis, endocarditis and myocarditis are all described as complications of epidemic meningitis due to the meningococcus. Their occurrence is rare in ordinary forms, but in the septicemic type they are much more common. Several cases are described by Herrick.[69]

Urinary.—A transient albuminuria sometimes accompanied by hematuria may occur in the course of the disease. This also is rare.

Cystitis may occur as the result of the retention which occasionally develops.

Arthritis.—Arthritis not infrequently develops during the illness. It may occur early or late. It usually attacks only one or two joints. While cases are described that go on to suppuration they are rare. The injection of serum into the joint has been tried in such cases. We have never done it. Indeed, we have never seen a case that did not clear up readily. Sometimes an arthritis occurring late has evidently been part of the serum reaction. It is due to a serous effusion into the joint tissue.

(Editor's Note.—Unilateral axillary adenitis reduced by cold—painful large groups of glands may develop.)

The varieties of arthritis that may occur have been thoroughly studied by Herrick and Parkhurst.[106] Of course it must be remembered that this study was made in an epidemic in which the septicemic type of meningitis predominated. They divide the different manifestations of arthritis into three types.

(*a*) An acute polyarthritis, developing as an initial or early symptom in the first three days of the disease. In most cases of this type, which usually occur with very severe infection, there is a profuse hemorrhagic rash, and the lesion is probably due to hemorrhages into the articular and peri-articular structures. There is little swelling and evidence of effusion but the joints are extremely painful and tender. Symmetrical joints are usually involved, especially the wrists, knees, ankles and elbows. The condition usually lasts about six days.

(*b*) A type of arthritis, usually involving only one joint and developing about the fifth day. In this form only a moderate degree of tenderness, redness, and limitation of motion occurs, but there is a great effusion and in the exudate the meningococcus is present in at least a third of the cases. The duration of the arthritis is from one to four weeks and recovery is complete but gradual. This type more commonly develops in the less severe types of infection.

(*c*) Serum arthritis.

2. Complications Involving the Central Nervous System.—These are very numerous and may be described under seven heads: (*a*) Secondary infections of the meninges; (*b*) miscellaneous conditions; (*c*) motor disturbances; (*d*) sensory disturbances; (*e*) psychic disturbances; (*f*) hydrocephalus; (*g*) complications involving the special senses.

The complications involving the nerves, according to Hutinel and Voisin,[86] are usually due to either of two causes, an inflammation of the nerves by extension from the meninges, or changes due to the organization of the fibrinous exudate; more rarely to meningeal or cerebral hemorrhages.

(*a*) *Secondary Infections of the Meninges.*—Although there are frequent references in the literature to mixed infections in meningitis, we have seen but a very small number, and these have occurred mainly just before death in some of the other forms of purulent meningitis, seeming to be a pre-agonal invasion. Indeed, we have seen the meningococcus appearing in the spinal fluid simultaneously with another organism in only four instances. In three instances, however, an epidemic meningitis has been followed in a short time by the invasion of the meninges by another organism. These three are as follows: The first patient, K. C., nine months, cleared up after four injections of serum and remained well for nearly two weeks. He then became suddenly worse, and the spinal fluid showed a pure culture of pneumococcus. The child died from pneumococcic meningitis. The second patient, R. R., three and one-half months, did not fully clear up clinically from the epidemic meningitis, though the culture of the spinal fluid became sterile. She was taken to a hospital, and a later puncture revealed the presence of streptococcus. The third patient, E. D., one and one-half years, was twice treated by us in the home. Further treatment was then refused. The child was taken to a hospital a few days later, and in about three weeks a Bacillus coli infection of the meninges developed. In the following four instances the meningococcus was present with another organism. In the first patient, J. L., nine months, the meningococcus alone was present in the first five fluids. In the sixth fluid a streptococcus also was present. It seemed that this secondary infection was from the blood as the child had a bronchitis at the time, and the streptococcus is not so likely to be due to accidental infection as is the staphylococcus or the B. coli. The second case, complicated by pneumonia ran a very similar course, a streptococcus appearing late in the disease. The case terminated fatally. In the third case the meningococcus and the staphylococcus aureus were both present in the first two fluids. The patient recovered with the use of antimeningitis serum. In the fourth case a paratyphoid bacillus appeared late in the course of the disease. The case terminated fatally.

(*b*) *Miscellaneous Conditions.*—Under this head may be described brain abscess, which is an occasional sequel of meningitis. A hemorrhagic condition of the brain or the meninges may also develop in the course of a severe meningitis. We have observed it in several cases. In one case, M. D., already described under the septicemic type, the first spinal fluid withdrawn was hemorrhagic. As the case reacted very severely to serum, the puncture was not repeated for some time. Fluids obtained later contained no blood. The patient finally recovered. In the case of W. H., also described before under the fulminating type, the fourth spinal fluid was hemorrhagic. The patient died 15 or 20 hours later. In the case of P. P., the first punctures showed a fluid free from blood. The second fluid was slightly bloody. The third fluid was still more bloody and the bleeding persisted, the blood oozing out of the puncture wound. This spot was cauterized with silver nitrate, and the bleeding from the puncture stopped for two days. When the bleeding reappeared, the patient was sent to a hospital where bloody fluid was obtained both by lumbar and ventricular puncture. The patient died. At first I was inclined to think the hemorrhage might have been due to some idiopathic blood condition, but later decided that it was probably a severe meningeal hemorrhage.

(c) *Motor Disturbances.*—To quote from Hutinel and Voisin,[86] the paralyses may be either flaccid or spastic and they may or may not be accompanied by muscular atrophy and sensory disturbances. They refer to hemiplegias accompanied by aphasia. In our experience paralyses, except for the muscles of the eye, both extrinsic and intrinsic, have been comparatively rare. In one case there was a paralysis of the arm that developed, became complete and cleared up within 12 hours. In several cases there has been stiffness of the arms and legs, especially of the leg, that has persisted for a short time after convalescence. It is quite possible that some of the cases of paralysis reported by the earlier writers have been due to poliomyelitis rather than to meningitis.

(d) *Sensory Disturbances.*—Sensory disturbances as sequellæ are rare. There may be a rather severe headache for a time after the meningitis has cleared up. The possibility of this being due to eye strain resulting from a weakness of the muscles of the eye should always be considered. A sciatica is occasionally reported as following an attack of meningitis.

(e) *Psychic Sequelæ.*—A rather common opinion exists among the laity and some physicians that children recovering from meningitis are very liable to suffer from mental disability. Indeed Hutinel and Voisin report several cases in which meningitis was followed by considerable mental impairment. Many writers on feeblemindedness give meningitis as the causative factor in a certain percentage of cases It has seemed to us, however, that error on this point might arise from the incorrect diagnosis of meningitis before lumbar puncture was in general use. We have, therefore, followed up a fairly large number of cases recovered from proved epidemic meningitis, and our experience has led us to believe that mental impairment following meningitis is rare. Epilepsy has been described, but it is very rare. We have never seen a case. [Ed. It may develop post hoc sed non propter hoc.]

(f) *Hydrocephalus.*—Hydrocephalus is not a very rare sequela of meningitis especially in young children. According to Dandy and Blackfan,[74] this may be due to either of two causes, a blocking off of the ventricles from communication with the subarachnoid space or a diminution in the rate of absorption of the spinal fluid due probably to a contraction in the size of the subarachnoid space resulting from adhesions. The first type of hydrocephalus exists of course in all cases of basilar meningitis with dry taps, and has been in our experience the more common.

(g) *Complications Involving Special Senses.*—The complications relating to the eye and ear are very serious and by no means uncommon. In fact, deafness is the complication that we fear most. Hutinel and Voisin refer to a case in which the sense of smell was lost following meningitis. We have never seen such a result.

In considering ocular symptoms and complications, these conditions are many and important. Netter and Debré give an excellent classification of these which is as follows: (1) Inflammatory and suppurative lesions of the conjunctiva, the interior of the eye and of the orbit; (2) complications due to the involvement of the nerves.

Under 1, are grouped: (*a*) Conjunctivitis and corneal lesions. Conjunctivitis is common but keratitis occurs only rarely. (*b*) Iritis and irido-choroiditis. Irido-choroiditis is the most serious eye complication. It goes on to ophthalmitis, loss of sight and atrophy of the eye-ball. Clinically, it is characterized at first by the presence of pus in the anterior chamber. (*c*) Orbital cellulitis. This is a rare development. We have never observed it.

Under 2, symptoms due to the involvement of the nerve, are grouped: (*a*) Disturbances of the internal musculature. The pupils are usually somewhat dilated. They ordinarily react to light early in the disease. This reaction not infrequently becomes sluggish or is lost at the height of the disease and returns during convalescence. The pupils are occasionally unequal. (*b*) Disturbance of the extrinsic musculature. Strabismus is rather common. It may be either external or internal. It is more often unilateral. Nystagmus occasionally develops. Complete ophthalmoplegia is said to occur. We have never seen it. Ptosis is rare. Diplopia may occur at intervals during the course of the disease. (*c*) Blindness—optic neuritis. Different authorities differ in regard to the occurrence of blindness and optic neuritis. Netter and Debré consider that total blindness with an optic neuritis progressing to optic atrophy is a not very infrequent complication developing either rapidly rather early in the disease or slowly in the later stages of the chronic type. They state that systematic examination of the eye grounds will reveal in many instances changes in the fundus varying from a papillary hyperemia to a papillitis and a neuroretinitis. These changes may last only a short time and be accompanied by little or no disturbance of vision.

Foster and Gaskell[3] did not find evidence of optic neuritis in any of 30 cases which they examined repeatedly. Sometimes blindness occurs with normal eye grounds. Sladen[81] cites such a case. We have not examined the eye grounds in our cases. The only instances in which we have observed blindness, however, have been in cases of basic meningitis or chronic meningitis shortly before death when it was difficult, indeed, to be sure whether or not the patient was really blind, and in the cases of iridochoroiditis mentioned before. In one case blindness occurred for a short time but cleared up completely.

Aural Complications.—Otitis media occurs occasionally in the course of epidemic meningitis. Often it is due to some other organism than the meningococcus. Sometimes it develops during convalescence.

Deafness is the most frequent serious complication of epidemic meningitis, especially in children. In young children it usually results in mutism as well. It develops in mild cases as well as in severe cases. It is usually bilateral, complete and permanent. It is often difficult to determine in the case of very sick children in what stage it comes on, but it usually develops rather early in the disease. In one case, however, it did not develop until three weeks after the last lumbar puncture when convalescence seemed well established. It came on very suddenly and was not accompanied by any other symptom. Otherwise, we might wonder if it were not due to a relapse. In a certain small number of cases, the deafness is not complete and clears up almost entirely during convalescence. The pathology of the condition has been discussed. It must be borne in mind that different epidemics seem to be attended by different classes of sequelæ and also that the percentage of cases in which sequelæ occur has been greatly diminished by serum treatment.

Following is a list of the complications and sequelæ observed by us in our first 500 cases:

Respiratory:	
Pneumonia	19
Influenza	4
Pleurisy	1
Urinary:	
Cystitis	2
Arthritis	13
Secondary infections of the meninges	7
Meningeal hemorrhages	5
Brain abscess*	2
Paralyses:	
Hemiplegia	6
Facial	6
Difficulty in speaking	3
Not classified	7
Headaches	3
Mental deficiency	1
Delirium during convalescence	2
Forgetfulness during convalescence	1
Hydrocephalus†	9
Eye conditions:	
Strabismus	30
Ptosis	4
Blindness from basic meningitis	3
Conjunctivitis	5
Iritis (unaccompanied by iridochoroiditis)	2
Irido-choroiditis‡	10
Exophthalmos	1
Ear:	
Deafness§	29
Otitis media	4

[*] Brain abscess probable in four or five other cases but necropsy not obtained.

[†] Hydrocephalus. In several other cases of basic meningitis in which death occurred the condition became well marked.

[‡] Iridochoroiditis in both eyes in one instance only.

[§] In several cases the deafness cleared up either wholly or in part.

Miscellaneous:	
Pachymeningitis	1
Contracture of arms and legs in a mental defective	1
Atrophy of thigh and calf muscles, absent knee jerks, partial ankylosis of spine in lumbar region	1
Stiffness of back	1
Neuritis	2
Pain in back and nervousness	1
Transverse myelitis	1

Treatment.—The treatment may be considered under three heads: Prophylactic, general and specific treatment.

The prophylaxis of a disease that apparently is spread mainly by carriers is much more difficult than in the case of diseases spread only by direct contact with the sick. At first thought, it would seem that the problem would be solved by isolating the patient, examining all contacts for carriers and isolating such as may be found, until they become negative. Further study shows it is more complicated. It seems, moreover, that carriers may develop from a casual contact with other carriers.

The question of carriers was studied very extensively by army workers during the World War. The latest reports show that no greater success has been achieved in attempts to disinfect them than has been attained in similar atempts with diphtheria carriers. In a recent communication Fieldes and Baker[107] point out that it is very rare for a carrier to develop the disease, and they add: "We conclude that the case of cerebrospinal fever is not specially responsible for the spread of the disease (unless there are spreaders in the vicinity) and is infected by one of the positive contacts. We look upon the case as one of those rare individuals who cannot confine the meningococci in the naso-pharynx and merely 'carry.'" In other words, it comes back to the question of individual immunity which most people seem to possess so far as epidemic meningitis is concerned, when we consider how few develop it in spite of being intimately exposed to it.

Although facilities may not always be at hand for the study of contacts and carriers, the practical prophylaxis can always be carried out by handling the patient with the same caution that would be used in any infectious disease in keeping away from the patient all persons not needed for his care and taking especial notice of the fact that the main danger of infection lies in the discharge from the nose and throat. Argyrol may be used in the nose and throat of the patient and contacts with the knowledge that it is non-irritating and is highly bactericidal for the meningococcus in vitro. By these means the number of carriers developing from a case would seem to be reduced to a minimum.

The possibility of actively immunizing individuals against epidemic meningitis by vaccination with killed cultures as in typhoid was tried to some extent in Texas and Kansas City in the epidemic prevailing in the southwest in the spring of 1912. Not enough work was done, however, to yield definite results. Indeed, considering the relatively few cases that develop in a community even in severe epidemics it will be difficult to prove the value of it. However, it seems worth trying. It was also used to some extent in the army camps. The dose used for immunization in the camps was 1, 2, and 3 billion at intervals of about a week.

General Treatment.—Epidemic meningitis is so serious a disease that no effort should be spared that may contribute in any way to the patient's recovery. A few words may be said in regard to the general care, and then we will deal more at length with the points that require especial attention. The patient should have a comfortable bed suitably made in a large, well-ventilated room, where he is carefully protected from drafts, as pneumonia develops very readily. If the patient suffers from photophobia or any eye complication or is very restless, it will be well if the room is somewhat darkened. If he is stuporous, care must be taken to turn him from side to side as bed sores develop quickly. Remembering that the meningococci are found in the secretions of the nose and throat, occasionally in discharges from the eye and rarely in the urine, one must exercise due care in the disposal of these discharges. The mouth and teeth must be carefully cleansed, and cleansing baths given with alcohol rubs, taking care to disturb the patient as little as possible.

The vomiting, which so constantly occurs early, rarely persists after the first 24 to 48 hours especially if lumbar punctures are begun early, and ordinarily demands no special treatment other than the calomel, the withholding of nourishment and the lumbar puncture. If it persists cracked ice may be given, and a mustard paste applied to the epigastrium. Bismuth subnitrate, sodium bicarbonate or cerium oxalate may be given. If these fail, atropin may be tried.

The three points that demand especial attention are the bladder, the restlessness and the feeding. As retention occurs rather often in meningitis it must be watched for very carefully, and the patient must be catheterized if necessary. Fortunately, the retention does not usually persist long. Hexamethylenamin is a good prophylactic for cystitis, and it has been recommended as having a certain influence on the progress of the disease. Sometime ago we gave it as routine. We do not feel at all sure that it has any disinfecting action on the spinal fluid. It may have some on the secretion of the nose and throat and certainly has on the urine. In some cases it has been followed by a hematuria, but a hematuria sometimes develops in the course of a meningitis without the drug.

If restlessness is present it must be controlled to some extent, at least, or the patient will rapidly wear himself out. An ice-bag to the head furnishes a measure of relief in some cases. Certain excellent authorities, Ker,[104] Hutinel and Voisin,[86] and others recommend hot baths repeated several times a day lasting from 10 to 20 minutes. We have not had an opportunity to try this method as most of our patients have been treated in tenement-house homes. In general, however, we have felt that moving the patient about in any way should be avoided as much as possible, and it would seem that repeated and rather long hot baths might have a somewhat debilitating effect. It has been our experience that if the restlessness does not yield to moderate doses of bromids, or bromids and chloral, it is better to use small doses of some preparation of opium, rather than risk depressing the heart by large doses of the bromid and chloral. Some patients will require very little sedative, perhaps none except during the reaction following the injection of serum. A measure of rest is very essential to the patient, and some means must be taken to secure it.

The feeding is most important. It must be rememberd that epidemic meningitis is a febrile disease that may be greatly prolonged, also that the amount of wasting is often peculiarly great. Therefore, as soon as the vomiting has stopped, the patient should be given as much liquid nourishment as he is able to take. This is best accomplished by giving small quantities frequently—every two hours. It should consist of milk with milk sugar added, malted milk prepared with milk, eggnogs, beef juice, broths, etc. Fruit juices in addition are often relished. The quantities given should be quite small when the vomiting has first stopped and gradually increased as it becomes evident that digestion is functioning more normally. As the patient improves, but before the temperature becomes normal, soft foods may be added, as junket, custard, blanc mange, ice cream, toast, etc. In the case of breast fed babies it may be necessary to express the milk and administer it with a medicine dropper.

No pains should be spared to meet the wishes of the patient in regard to food, and it will be found that he can usually take a *small* quantity of almost anything he may desire. If the retraction of the head becomes so marked that swallowing is impossible, it will be necessary to feed by a nasal tube. Fortunately, this is very rare. Indeed, we have never found it necessary to resort to it. By using a high caloric diet, the patients in fairly short cases of meningitis recover with very little wasting, and a degree of reserve strength is built up for the chronicity that sometimes develops in instances in which a favorable progress early had led us to hope for an early and favorable termination. Quite as much as in typhoid is the high caloric feeding desirable in meningitis. As in any disease the various symptoms and complications must be treated as they arise. Cardiac stimulation may be necessary at times, and the particular drug to use would depend on the individual indication. We often use caffein sodium benzoate or digitalis. Strychnin is, of course, contra-indicated.

Maclagan and Cooke[66] suggest the intravenous or intramuscular, not subcutaneous, injection of from 10 to 20 m. of adrenalin, 1:1000, every four hours in fulminating cases, as their necropsy work has shown that in these cases there is hemorrhage into the adrenals. They report several cases in which this medication seems to have been of value.

The eye complications require appropriate treatment by a specialist. In cases of conjunctivitis uncomplicated by an iritis or irido-choroiditis, argyrol and cold applications are beneficial. At the first appearance of an iritis or irido-choroiditis, however, the pupil should be dilated with atropin, to prevent the formation of adhesions, and hot compresses should be used. Argyrol is useful in these conditions also, as conjunctivitis is usually present. In addition to the symptomatic treatment Netter[2] advised, in the case of irido-choroiditis, the injection of antimeningitis serum into the vitreous. One case that he thus treated with a few drops of serum cleared up. We have never tried it. Otitis media develops occasionally during the course of meningitis and requires appropriate treatment. The joint conditions usually clear up with symptomatic treatment.

Lumbar Puncture.—While lumbar puncture is a comparatively simple procedure, it requires training and practice to do it easily and well. If skillfully done it does not cause the patient great pain, and there is a minimum of bloody fluids. A Quincke needle of medium caliber—size 15 or 16—and rather blunt is suitable for most cases. It is well to have a smaller and larger needle at hand—the smaller for rare instances when the intraspinal space is very narrow, as may be the case in infants, the larger for very thick purulent fluids. The gravity apparatus for the administration of serum is very easy to make. It consists of the metal connection which fits the needle when the stilet is removed, a piece of small rubber tubing 15 to 18 in. long and the barrel of a syringe, a 15-c.c. centrifuge tube with the bottom sawed off, or a small funnel. It is well to cut the rubber tubing near the metal connection and insert a piece of glass tubing so that one can see the serum running in or the fluid running out if, as sometimes happens, one connects the gravity apparatus while the fluid is being withdrawn to prevent its escaping too rapidly. The importance of strict asepsis in performing lumbar punctures seems to be often ignored. We have called attention to this in previous articles, and Regan[108] has emphasized it. While the percentage of secondary infections, even with a rather careless technique, may be small, the result of such a secondary infection with the staphylococcus, B. coli, etc., is so highly fatal that the failure to take every reasonable precaution is most reprehensible. It is essential, therefore, that the apparatus be carefully boiled; and that the site of operation be disinfected, preferably with iodin; that sterile towels, or better towels wet with bichlorid, be spread over the patient's hips and around the field of operation, so that the operator may touch the patient and locate the landmarks without contaminating the hands, and that the hands of the operator be disinfected and remain sterile throughout the operation. As routine we prepare a basin of warm bichlorid which serves to disinfect the towels and the hands of the operator and also to warm and disinfect the bottles of serum. This enables the physician to fill the gravity apparatus with serum without contaminating his hands or risking the contamination of the serum.

We do not use a general anesthetic, as it does not seem to be necessary, and we feel that it increases the liability to pneumonia. When the lumbar puncture is skillfully done the patients do not complain greatly of the pain, and it is desirable to have the patient's subjective symptoms as a guide in withdrawing the fluid and injecting the serum. We do not ordinarily use a local anesthetic. It is in itself somewhat painful and the preparation only adds to the patient's nervous tension. When it is desirable to use a local anesthetic ethyl chlorid is to be preferred to cocain as its application is less painful, and it does not obliterate the landmarks by producing an edema as cocain does. In cases when daily punctures are necessary, as in epidemic meningitis, the use of a local anesthetic is not to be advised as it is likely to add to the irritation of the back. It is of the first importance in cases of epidemic meningitis that the back be kept in good condition. This end seems to be attained more frequently if the iodin is painted on the dry skin not too thickly and allowed to evaporate rather than washed off with alcohol. We usually cover the point of puncture with a piece of sterile cotton fastened by a single strip of adhesive. The angle of adhesive has to be changed from day to day to prevent the skin beneath from becoming sensitive. By this method we can usually perform daily punctures 10 or 12 times or more, and yet keep the back smooth and comfortable.

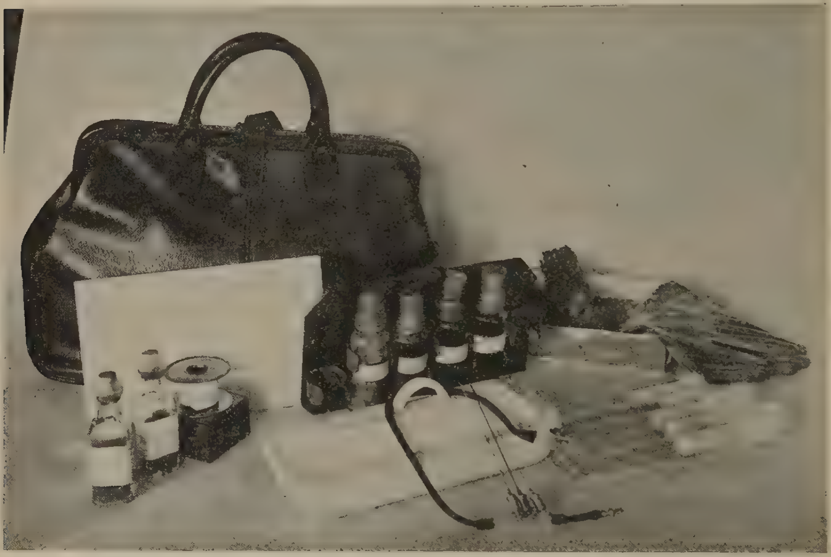
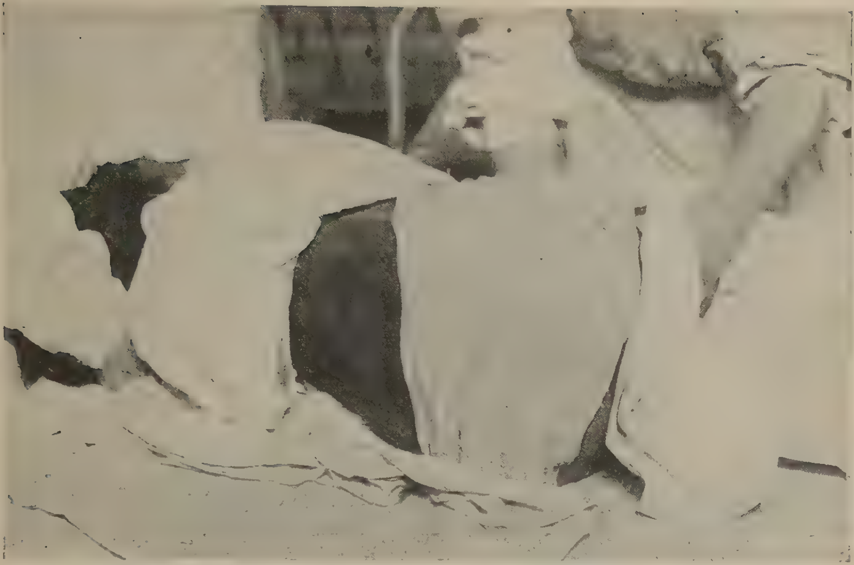


FIG. 77.—Equipment necessary for lumbar puncture and administration of serum.

The position of the patient is also of great importance. A lumbar puncture should be done with the patient lying down, unless one is sure that the pressure of the spinal fluid is not much increased. It is evident that when the patient is sitting, the pressure is increased by the length of a column of water from the ventricle to the point of puncture. This column added to an already increased pressure may result



Figs. 78–81.—Showing steps in lumbar puncture and administration of serum.

Fig. 78.—Patient held in position—back flexed—sterile towels surrounding field of operation. Field of operation painted with iodine. *Note marks of previous lumbar punctures.*

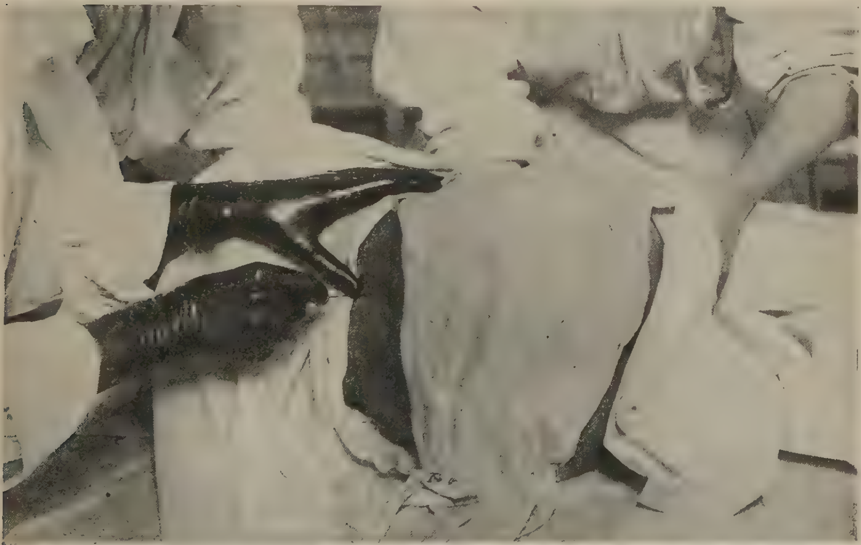


Fig. 79.—Needle being inserted—operator is wearing sterile gloves—and towel which operator's hand is touching is sterile.

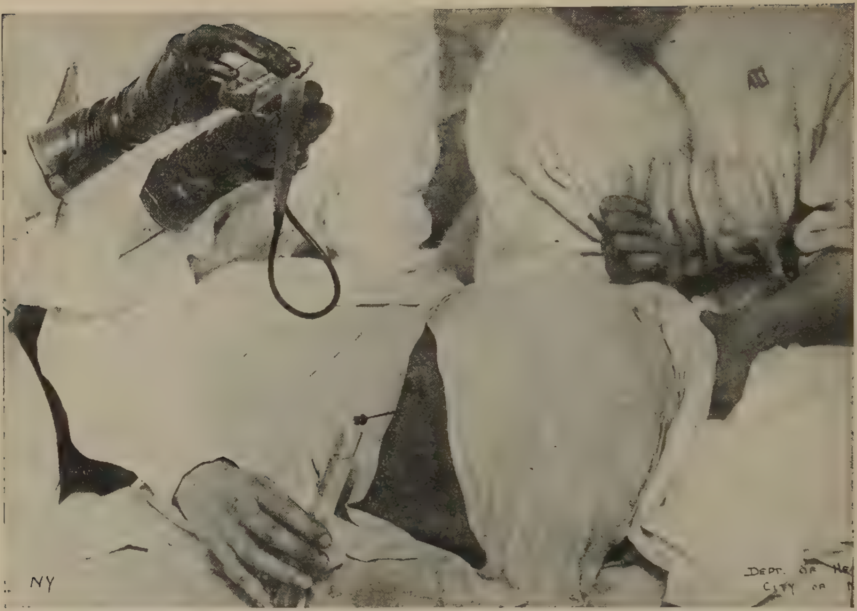


FIG. 80.—Spinal fluid being collected in test tube—at same time operator is filling gravity apparatus with serum.

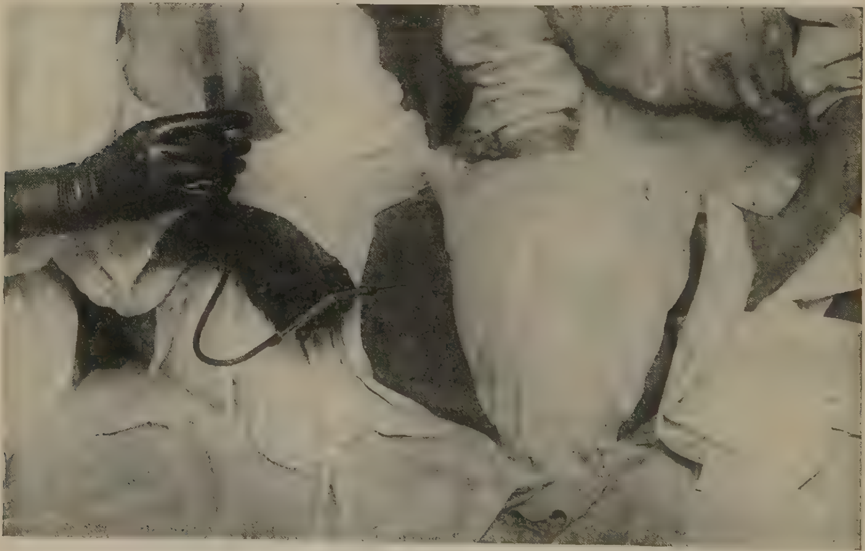


FIG. 81.—Serum introduced by gravity.

in too rapid lowering of the pressure. The patient should be held with the knees drawn up against the abdomen and the shoulders drawn forward, thus arching the back and separating the spines of the vertebræ as much as possible. The vertebral column should be parallel to the bed or table on which the patient lies, and the plane of the back at right angles to it. A patient who is not delirious will often hold himself in a very good position by clasping his hands back of his knees. If the patient is delirious it may be necessary to make a rope from a sheet and pass it back of the neck and under the knees. Care spent in getting the patient in a proper position and seeing to it that he is securely held will be amply rewarded by the greater ease in performing the lumbar puncture. The site of the puncture having been painted with iodin and the hips of the patient and the immediate surroundings of the field of operation having been covered by sterile or antiseptic towels, the notch most nearly coinciding with a line drawn from crest to crest of the ilium is selected. The puncture is usually best made in the median line, and the needle usually points a little upward as it goes in. Its direction will depend, of course, on the relations of the spinous processes, and these are subject to considerable individual variation. The depth to which the needle penetrates varies greatly with the age and the development of the patient. A very distinct feeling of decreased resistance is felt as the needle enters the canal. When this occurs it is well to stop and withdraw the stilet, though it may be necessary to go a little deeper to penetrate the dura, particularly if it is not distended with fluid. Care should be exercised not to push the needle in too rapidly and hit the anterior wall of the canal as a bloody fluid often results. It is very difficult to avoid doing this in young infants, especially when the dura is not distended by fluid and is carried on in front of the needle. In some cases of this sort a small sharp needle seems to work better, but in general we get blood much oftener with a sharp than with a blunt needle, and a very small needle is unsatisfactory if the fluid proves to be purulent. Another cause of bloody fluids or unsuccessful taps that we have observed is selecting a space lower down than that on the line with the crest of the ilium. It would seem that the interior of the canal is more vascular at these lower levels. Very rarely we find a patient whose back is very rigid or whose intervertebral spaces are narrow. It is then necessary to make the puncture a little to one side of the median line. These cases are rare, however, as mentioned, and the technique is simpler when one makes the puncture in the median line. The steps in lumbar puncture and the administration of serum are shown in the accompanying illustration.

It was formerly taught that only from 10 to 15 c.c. of fluid should be withdrawn ordinarily. If punctures were done with the patients sitting up, this would doubtless be a safe rule. With the patient lying down we are accustomed to allow the fluid to escape until the pressure is evidently about normal as shown by the fluid flowing slowly, drop by drop, perhaps to 10 or 15 drops per minute, unless the patient complains of severe headache or shows other untoward symptoms, or unless we have reason to suspect brain tumor. We are taught that there is danger of sudden death in cases of brain tumor, from the medulla being forced down into the foramen magnum with a decrease in pressure. We have had little experience with brain tumors. The question of possible dangers from lumbar puncture and the administration of serum will be discussed later. We have withdrawn over 100 c.c. of fluid in cases of meningitis or meningism without discomfort to the patient during or after the puncture. If the fluid is escaping very rapidly it is sometimes well to attach the gravity apparatus and by raising it retard the flow and prevent a too rapid decrease of pressure.

Failure to obtain fluid may be due to a variety of reasons. The most obvious reason is failure to strike the canal. Other reasons are, pushing the dura in front of the needle as may happen if it is not distended with fluid, a slightly rusty needle which prevents the fluid from running through it if the pressure is low, or a pressure so low that the fluid will not run out at all with the patient in a horizontal position. In this case fluid may be obtained if the head is somewhat elevated. Then, too, it happens not so rarely in cases of purulent meningitis that one gets a dry tap, due apparently to the amount of spinal fluid being small and somewhat sticky in consistency, so that it does not flow out. Serum flows in, however, as readily as if a considerable amount of fluid has been withdrawn, and the serum will show variations in pressure depending on respiration. This may happen once or even several times in the course of an epidemic meningitis, and yet the case will go on to a favorable outcome. It will be discussed more at length under ventricular punctures.

When a basilar meningitis is present, however, and there is a walling off of the ventricles not only does one get no fluid or at most a few drops but only a very small amount of serum, 2 to 3 c.c., will run in and that not easily. In these cases changes in respiration will not be registered by the serum in the gravity apparatus. Another cause of failure to obtain fluid is that the fluid may be too thick and purulent to flow through the needle. If this is suspected gentle suction with a syringe may be cautiously tried, and a little serum or sterile saline may be injected, great care being exercised to avoid exerting undue pressure.

The Administration of Serum.—If a cloudy fluid is obtained or if in the first 24 to 36 hours of illness the fluid is clear and despite this the clinical signs strongly point to meningitis, especially in time of an epidemic, anti-meningitis serum should be administered at once. In the case of cloudy fluids, if the meningitis is due to some other organism than the meningococcus, the anti-meningitis serum will do no harm, and the early administration of serum if the case is one of epidemic meningitis is highly desirable. In the case of clear fluids if the condition is one of meningism or poliomyelitis, the serum will cause some meningeal irritation, which will, however, soon subside. The risk is worth taking for the sake of securing the very early administration of serum, if the symptoms are particularly suggestive of epidemic meningitis. Further treatment, of course, will depend on the examination of the cerebrospinal fluid.

We feel very strongly that serum should always be administered by the gravity method devised by Koplik,[109] never by a syringe. With a syringe, it is quite impossible to feel sure that one is not unduly increasing the intraspinal pressure, even though the serum is administered very slowly. Indeed most accidents recorded following the administration have occurred when a syringe has been used. With the gravity method, one is certain that the intraspinal pressure is not greatly increased and yet by pressing along—"milking"—the rubber tube, enough force may be exerted to clear the needle if it is obstructed by a little pus or fibrin. Moreover, the ease with which the fluid runs in is best indicated by the gravity method and is a valuable guide to dosage. The serum should be warmed to body temperature before being injected.

Size of the Dose.—More or less difference of opinion exists as to the size of the dose of serum. Some writers believe that large doses—30 to 40 c.c. or even more—should be administered, if as much or more fluid was removed. Other writers lay down a rather fixed dosage, depending on the age of the patient. We are inclined to take issue with both. During the first two years that we were working on meningitis, we used rather large doses of serum as routine, if as much or more fluid was withdrawn. At that time, we not only had a far higher mortality than we have had of late, but it occasionally happened that in spite of the serum being injected by gravity, the patient went into shock, and while only two fatalities have followed administering serum more than 4000 times, the effect of the shock on the family, the patient and ourselves was decidedly unpleasant. We do not believe that the serum was the cause of these fatalities. This point is discussed later.

It is our usual custom to give at first a dose of 20 c.c., if as much or more fluid has been withdrawn and if the serum runs in readily. If the response to two or three doses of this size is not satisfactory, the amount is cautiously increased to from 30 to 40 c.c. depending on the flow of serum by gravity and on the amount of fluid removed. It is a good general rule to give a quantity of serum less than the fluid, but like most rules, it has exceptions. It occasionally happens that a quantity of serum larger than the amount of fluid withdrawn may be given advantageously, if it runs in readily. Indeed, as it was previously stated, in the course of cases of epidemic meningitis, a dry tap is sometimes encountered, and yet serum flows in with perfect ease. In such cases, 5, 10 or even 15 c.c. of serum may be given. The patient should be watched in such cases with extreme care, however, for any untoward symptoms, especially for changes in the pulse and respiration. The age of the patient usually affects the size of the dose very little, we think. A very young child can often be given 20 c.c. of serum if as much fluid has been removed. Netter and Debré,[2] Dopter,[87] Dunn[110] and Koplik[109] advise even larger doses, 30 c.c. or more. At first thought it may seem illogical to give a young child as large a dose of serum as an adult would receive. It must be remembered, however, that the ratio of the size of the head of a child to the head of an adult is in no way in proportion to the body-weight, also that the serum being curative but not toxic the dose need not be decreased for fear of poisoning the smaller individual and, moreover, that as large a quantity of spinal fluid is often withdrawn from young children as from adults and the serum runs in as readily.

Repetition of Serum.—As regards the repetition of the serum there is also a difference of opinion. Some physicians give one or two doses and then wait until the patient is worse before continuing. Others advise giving it in large doses every 12 or even every eight hours, until a degree of improvement takes place. From a theoretic standpoint, it is difficult to say whether or not the administration of serum every 8 to 12 hours should be better than every 24 hours. While the exact action of the serum is not known, it is believed to exert both a bacteriotropic and a bactericidal influence, the bacteriotropic action being probably the more important. In just what dilution this action may take place, how long it takes the cells to react to their maximum phagocytic power and how long this power is retained by them we do not know. From work done by Dochez and Horn, it is probable that all the serum is not excreted from the spinal canal for about 24 hours. Of course, it becomes greatly diluted before this time. It is not at all improbable, however, that cells still having a high phagocytic power may be withdrawn by a puncture eight hours or so after the serum is administered. We do know that the administration of serum is, in a large percentage of cases, followed by a reaction, which begins in from two to eight hours and continues for eight or more, as a rule. This reaction is ordinarily characterized by a rise in temperature, and increased headache and restlessness. Just what relation to the therapeutic action of the serum these manifestations have I do not know, but I have always questioned whether it were advisable to do a lumbar puncture and give serum before this reaction had passed.

It has always seemed well to me to keep in mind the fact that we are treating the patient as well as the disease and that very frequent and large intraspinal injections may be harmful to the patient to such an extent as to overbalance any possible benefit from an increased concentration of the serum. Doing a lumbar puncture and giving serum is a procedure that subjects a patient to some disturbance so that on this basis alone its too frequent repetition is not desirable. Here, again, we pursue a conservative course and *usually* give serum only once in 24 hours. We feel that while there are exceptions to all rules the following three are safest in the great majority of cases.

1. Repeat the injection of serum daily until the fluid is free from meningococci, as shown by a 48 hour sterile culture, even if the symptoms clear up with extraordinary rapidity.

2. It is rarely safe to give less than four injections of serum, even if the second culture is sterile and if the symptoms are greatly improved.

3. After the culture becomes sterile, if the symptoms have not greatly improved, punctures should be done and the serum administered but not necessarily every day. The clinical conditions of the patient should be the guide. With this method of treatment Worster-Drought and Kennedy[111] agree in general. They use larger doses—from 30 to 45 c.c., usually 30—for patients over 15 years of age.

In connection with the question of dosage and the frequency of repetition, it is interesting to note the army experience of Major Henry W. Jackson, for some time connected with the Meningitis Division of the Health Department of New York City. When cases of meningitis began to develop at the camp where he was stationed, the medical officer in charge at first insisted on the intensive method—large doses at frequent intervals. As Major Jackson had been in the habit of using a more conservative method of treatment with good results he finally persuaded the commanding officer to allow him to run parallel cases with the two methods with the result that the intensive method was discontinued. This is particularly instructive because it shows the results obtained by the two methods tried under identical conditions.

Sometimes during convalescence it may be necessary to do one or more punctures to relieve pressure, no serum being administered. This is practiced especially if the fluid is becoming normal as shown by a good reduction of Fehling's, and a decrease in albumin, globulin and number of cells, as well as by the sterility. If the fluid is still cloudy with greatly increased globulin and albumin and especially with a poor reduction of Fehling's, we think it wise to continue the administration of serum, for we feel that such fluids may be due to a continuation of the inflammatory reaction, perhaps deep seated or walled off in some way so that the organisms do not escape into the fluid and that under these conditions the serum may be of some benefit.

The most common mistakes in serum treatment of epidemic meningitis seem to consist in being too optimistic and giving too few doses of serum if the patient improves considerably after the first one or two injections, and not being hopeful enough and, therefore, failing to persist with the serum if the improvement is very slow. It has been the experience of the meningitis department during the past thirteen years that it is rarely safe to give less than four doses of serum on consecutive days.

In cases which have been running on for some time and in which the patients are evidently improving when first seen, two or three injections may be sufficient. A case of average severity usually requires from five to seven or more injections. It is safer to give the injections on consecutive days until it seems evident that the patient is out of danger than to skip a day or two when a slight improvement occurs, thereby giving the organisms a chance to increase.

Some physicians feel that if a rather small number of injections, perhaps four or six, is not sufficient to clear up the case, it is useless to continue with the serum. Our experience has not led us to agree with this view. We have had cases in which 15, 20 and even 28 injections were necessary to produce a cure, and we feel that the patient recovered because of rather than in spite of the injections, since in several instances when the injections were interrupted on account of the objections on the part of the patient or family the patient promptly became worse. We are not in the habit of giving serum oftener than every 18 to 24 hours in ordinary cases. In an extremely severe case to or three injections, at 12 to 18 hour intervals, may be advisable.

While the early administration of serum is very desirable the response to it of patients that have been ill for two weeks or more is often highly satisfactory and affords excellent clinical evidence of the therapeutic value of the serum, since these cases have had the opportunity to clear up spontaneously and have failed to do so. Hence, we should in no way be deterred from the administration of serum because the case is seen late. This point seems worth emphasizing for we occasionally meet physicians who feel that serum is of little value unless used early.

Intravenous Serum Therapy.—The use of antimeningitis serum intravenously has been strongly recommended during the past two years. Of course, this method is indicated only in cases of meningococcus sepsis, and should always be combined with intraspinal injection unless it is definitely proved that a meningitis is not present. That the intravenous use of the serum must never displace the intraspinal injection in the presence of a meningitis must be kept in mind, as a casual study of the recommendation of intravenous serum therapy has led some physicians to feel that it is an improvement on the intraspinal method—not an additional procedure indicated only in a certain type of case. It should be emphasized that while it is commonly accepted that the meningococci may be found in the blood early in most cases of epidemic meningitis, this by no means constitutes a menigococcus sepsis. In the vast majority of cases, they disappear speedily from the blood stream.

The intravenous method has been most thoroughly worked up and applied by Herrick[69] at Camp Jackson but, of course, was used there by him with adults only. He recommends from 50 to 120 c.c. repeated every 12 hours until the temperature becomes normal or until six or eight injections have been given. In severe cases the serum is repeated every eight hours. He advises that the first 15 c.c. of serum be given at the rate of 1 c.c. per minute. With this intravenous treatment he combines serum intraspinally in all cases in which a meningitis is present. Herrick[69] feels that these large doses may be safely employed, indeed, that small amounts may have a harmful effect on the disease.

Golden,[112] on the other hand, reports severe reactions following even 20 to 40 c.c. of serum.

Netter,[113] referring to cases of the septicemic type, wrote in 1916; "We do not believe that intravenous injections are indispensable, as they are incontestably more dangerous, since they have many times under our eyes provoked accidents and once even death. We advise employing, at least in the beginning, intraspinal injections which are certainly less dangerous and which have sufficed to cure the greater part of our patients." Debré and Lemaire[114] have shown that serum injected into the spinal canal appears extremely quickly in the blood. In 1918 Netter repeated practically the same advice. Blackfan,[115] also, warns against the intravenous use of serum in children. Our own experience with this method has not inclined us in its favor, but it has been too limited to form any very decided opinion. However, the word of Netter,[113] who has had a wide experience with meningitis extending over many years and including all ages and types of case, and that of Blackfan, must carry great weight.

It is generally recommended that when intravenous injections are employed the patient should be tested for sensitiveness to serum, and if it exists that he should be desensitized. The method for testing for sensitiveness is the intracutaneous injection of from 0.1 to 0.05 c.c. of serum diluted to 1 c.c. with normal saline. The reaction showing sensitiveness consists in the formation within a few minutes of a wheal around the point of injection. Bezredka's method of desensitization is as follows: 5 c.c. of the serum is diluted to 50 c.c with normal saline; of this 1 c.c. is slowly injected intravenously. Four minutes later 3c.c. is injected; two minutes later, 10 c.c., and again in two minutes, 25 c.c. In 15 minutes the full therapeutic dose may be given, according to this theory. In practice, however, one cannot absolutely rely either on the test for sensitiveness nor on the efficiency of the method of desensitization. It is a fairly safe procedure to dilute the first 5 or 10 c.c. of serum to be injected three or four times with normal saline solution and to proceed very slowly. Allow only a few drops to run in and then wait a minute. Follow with 1 c.c. and wait for a minute or two, and so on so that at least 15 minutes are consumed in giving the first 15 c.c. of the diluted serum. If no symptoms have developed by this time, the remaining portion of the serum may be given more rapidly, and it need not be so much diluted. The temperature of the serum should be at the temperature of the body when it is injected.

If symptoms of distress appear such as cyanosis, rapid pulse and dyspnea, the injection of an appropriate dose of adrenalin chloride or atropin has been recommended.

Ventricular Puncture.—Ventricular puncture is rather freely employed by some physicians when spinal puncture fails. As stated in a preceding paragraph, one or more dry taps are not infrequently encountered in cases of meningitis in which it is very evident that there is not a basilar condition. A fair proportion of these cases clear up when a lumbar puncture is done regularly, and serum is administered in varying amounts—5, 10, 15 c.c., depending on the ease with which it runs in and the absence of untoward symptoms on the part of the patient. During the first seven years of our experience with serum, there were 27 cases with dry taps, of which 17 were fatal. Of these 17, seven had ventricular punctures. Of the 10 that recovered, one was given intraventricular treatment in a hospital rather against our advice, since the diagnosis was in doubt.

During the past four years we have seen four cases of rather unusual interest. In one case, a child of nine months developed toward the close of treatment a mild degree of hydrocephalus, with repeated dry taps. It was taken home from the hospital with a rather bad prognosis. When seen later, however, it was observed that the hydrocephalus had not progressed and the child had developed fairly well. Another child of six months showed the same condition toward the end of the illness. One ventricular puncture was done, the fluid being clear and sterile but the fontanelle soon became tense and it was advised that the child be taken to a hospital for special treatment. This was not done, however, and when seen some months later there was still a moderate degree of hydrocephalus, though the child's general condition was good. A year and a half later she developed pneumococcic meningitis from which she died. A lumbar puncture at that time showed that the adhesions had disappeared, as a large quantity of fluid was obtained. These are the only two cases of well-defined basic epidemic meningitis under our observation in which recovery has taken place, that is, cases showing well-defined pressure symptoms, bulging fontanelle, and dry taps, when the serum failed to run in. Dandy[116] mentions a similar case of spontaneous cure of hydrocephalus. The third case was that of a baby three weeks old, with epidemic meningitis. Early in the treatment the quantity of fluid became very small and only small amounts of serum could be given. After three or four treatments when this happened a ventricular puncture was done and fairly large amounts of only slightly cloudy spinal fluid, containing the meningococci were withdrawn, serum being administered at the same time. After this procedure had been repeated several times a lumbar puncture was done and we were much gratified at being able to withdraw 20 to 25 c.c. of fluid and the fontanelle ceased to show signs of pressure. On the following day, however, the adhesions had apparently formed again, as only a few drops of fluid could be withdrawn and the fontanelle continued to bulge. Ventricular punctures were necessary thereafter on account of the pressure, the fontanelle usually becoming tense in 12 to 18 hours after the fluid was withdrawn. On one occasion, however, it remained flat for over two days and we again entertained a false hope that the inflammatory process at the base of the brain had subsided and that a cure had been effected. The condition became progressively worse, though the fluid became sterile fairly early, and death finally resulted.

It should be noted that one may fail to obtain fluid by lumbar puncture either because the fluid is so thick and purulent that it will not run down the rather small space in the spinal canal or because adhesions have formed at the base walling off in the ventricles fluid that is not very purulent. This latter condition was evidently present in the case just described while the former condition obtained in the case which follows—a meningitis due to the colon bacillus, which I will mention briefly on account of the unusual course. This occurred in a baby three weeks old. The fluid was so thick that it could be obtained only by ventricular puncture. It was by far the most purulent cerebrospinal fluid I have ever seen, a test-tube full when allowed to stand being almost pure pus with only perhaps ½ in. of clearer supernatant fluid. It was also hemorrhagic in the first 12 or 15 punctures. Very large quantities, frequently 75 to 100 c.c., were removed. The baby's condition, at first desperate, improved much more rapidly than did the fluid which continued to be very purulent and showed on culture the colon bacillus in the first 15 fluids. At many of the ventricular punctures irrigations of saline were used to wash out additional quantities of pus, which would not drain off, and an autogenous vaccine was administered into the ventricle. The principle underlying this vaccine treatment is discussed under treatment. Finally, however, the fluid became sterile, gradually clear and less in amount. After about 30 ventricular punctures it was practically normal. Two or three lumbar punctures were then done, fluid being easily obtained and accompanied by a softening of the fontanelle, which did not at this time show undue tension. For two months and a half the baby's condition seemed excellent. His weight increased normally, he slept well, laughed and seemed to have made a perfect recovery. Then suddenly hydrocephalus developed and only a few drops of fluid could be obtained by lumbar puncture. Ventricular puncture yielded large quantities of clear, sterile, practically normal fluid. A puncture of the corpus callosum was considered but was advised against by an authority on brain surgery. This is the only case in my own experience and I have been able to find no duplicate in the literature, in which such a long period of apparent good health intervened between the end of treatment and the development of a hydrocephalus.

The reports of recovery after ventricular punctures are comparatively few, and we feel that some of them may have taken place in the type of case to which we have been referring, in which, although one or more dry taps may occur, there is not a true basilar meningitis. As our own results show, many such cases will clear up under the more conservative treatment. We feel, therefore, that ventricular puncture is not a procedure to be resorted to without very clearly defined indications of the presence of a basic meningitis. The danger of a secondary infection is probably greater with a ventricular than a lumbar puncture on account of the tendency of scalp wounds to remain open and the closer proximity of the meninges to the surface. Moreover, we do not know what harm may be done by the injury to the brain substance. In one case of recovery after ventricular puncture the result seems to show that injury to the brain may have been done by the ventricular puncture. For the report of this case we are indebted to Dr. L. W. Sauer of Chicago.

In June, 1914, J. P., aged seven months was seen, having been ill for five days, with vomiting, rigidity of extremities and neck and fever. The child was seen by another physician and was sent to the Children's Ward, Evanston Isolation Hospital.

Physical examination showed a rachitic, pale, rather poorly nourished girl baby with bulging fontanelle, marked opisthotonus, reflexes somewhat lively, Babinski, Brudzinski, etc.; lungs, heart, abdomen, mouth and ears negative.

Spinal puncture yielded a rather thick, cloudy fluid, not under much pressure. Examination showed Gram-negative diplococci intracellular and extracellular. Cultures from the nose showed similar diplococci. Twenty cubic centimeters of serum—New York Department of Health—were administered. Puncture was repeated and 20 c.c. serum given that night, and next morning no fluid would flow even from an interspinous space above one last used. Not much edema was present in lumbar region. The spines were easily palpable. A ventricular puncture was made showing fluid much more liquid than that from spinal canal the night before. Twenty cubic centimeters of serum were administered into the ventricle, which was repeated that night and next day.

The child made an uneventful recovery and was discharged two weeks after entrance. Two other children in the family had Gram-negative diplococci in nasal cultures, but never contracted the disease.

Since the discharge from the hospital in 1914, the child was re-admitted on two occasions, first for severe dysentery (with blood and pus), and second, for bronchopneumonia with pertussis.

The child is now about four years old, looks like a child of two; sits with difficulty; cannot stand or walk; the lower extremities are nearly infantile; reflexes absent, muscles flaccid, but child can move legs at will. Cannot feed herself although arms are apparently quite normal. Her weight is about 30 lb. The visiting nurse says that for a time after the discharge from the hospital the child acted as if it could not see, but this has improved. The mentality is that of an infant. She does not talk, nor is there bowel or bladder control. In short, the child is a helpless imbecile.

In view, therefore, of the small number of recoveries with ventricular puncture, the greater danger of secondary infection and the possibility of subsequent impairment to the mentality, we feel that ventricular puncture in epidemic meningitis is a procedure the use of which should be made only as a last resort.

Ventricular Puncture.—The technique is as follows: The scalp should be carefully sterilized. The puncture is made near the lateral angle of the anterior fontanelle, about 2.5 cm. (1 in.) from the median line. The needle is pointed downward and slightly inward to a depth of about 3 cm. (1¼ in.). An ordinary lumbar puncture needle is used, and if the fluid withdrawn is cloudy, anti-meningitis serum should be injected at once by gravity. It may be necessary to puncture both ventricles, and if so this is usually done on alternating days. Every precaution must be taken to prevent infection.

In adults and older children trephining is necessary. For this Keen's method may be used. The trephine opening is made at Keen's point, 3 cm. (1¼ in.) above the external auditory meatus. The needle is directed toward the upper border of the pinna on the opposite side, and enters to a depth of about 5 cm. (2 in.). By this method the most dependent portion of the ventricle is entered. Here again, it may be necessary to trephine on both sides so that both ventricles may be punctured.

Puncture of the Cisterna Magna.—Puncture of the cisterna magna (that is, puncturing between the occipital bone and the first cervical vertebra, through the occipito-atlantoid ligament) has been used by various workers to obtain fluid in laboratory animals.

Wegeforth, Ayer, Essick[117] and others have used it quite extensively in human beings also. They suggest it as a means of irrigating the spinal canal in cases in which the fluid does not flow out well by lumbar punctures, due either to a very purulent fluid or to adhesions along the spinal canal. In these conditions it is indicated. Of course, it is obvious that it does not take the place of ventricular puncture in cases where there are adhesions at the base of the brain, confining the fluid to the ventricles. It may be tried, however, in any case where there are repeated dry taps, as it is not easy to determine where the block is located, unless there are facilities for injecting oxygen and taking radiograms. Although accidents following the use of the cisterna punctures have not been reported, the proximity of the needle to the medulla imparts certain elements of risk to the operation. It would seem that it should be attempted only by those who have had ample practice on cadavers and on laboratory animals and that it should be used only on patients who are under an anesthetic or on those who are so stuporous that any sudden movement on their part is improbable. At least, this has been my own policy in using the operation.

The technique is described by Ayer[121] as follows:

The patient is placed on the side, as if for lumbar puncture, with neck moderately flexed. Care is taken to maintain the alinement of the vertebral column to prevent scoliosis and torsion, and in cases where comparative pressure readings are important the lumbar and cisterna needles should be on the same horizontal plane. After antiseptic preparation of the skin, usually including the shaving of a little hair, and local anesthetization with procain, the thumb of the left hand is placed on the spine of the axis, and the needle inserted in the midline just above the thumb. The needle may be pushed rapidly through the skin, but should then be cautiously and guardedly forced forward and upward in line with the external auditory meatus and glabella, until the dura is pierced. If the cisterna be entered at this angle there is usually a distance of from 2.5 to 3.0 cm. between dura and medulla as shown on frozen sections; with the needle less oblique in position the distance between the walls of the cisterna becomes progressively less. Therefore, it is good practice to aim a little higher than the auditory meatus, and, if the needle strikes the occiput, to depress just enough to pass the dura at its uppermost attachment to the foramen magnum. At its entrance the same sudden "give" is felt as in lumbar puncture.

The needle employed is a regular lumbar puncture needle, nickeloid, 18 gage preferred, with beveled stilet, sharp on the sides but not too sharply pointed. There is rather less variation in the depth of the tissue traversed than in the lumbar region, being in an ordinary sized adult from 4 to 5 cm., the greatest distance in the series being 6 cm. and the smallest 3.5 cm. It was found that a faint circular scratch on the needle, 6 cm. from the tip, was entirely satisfactory in judging the distance, and was preferable to the deeper markings of the Patrick needle which tend to make its insertions a little jerky and consequently less guarded.

Vaccin Therapy.—Autogenous vaccins have been used to some extent in treating meningitis, especially in those cases that tend to run a chronic course. We have not used them sufficiently to speak with assurance as to their value, but in some cases they have seemed to be of benefit. It seems necessary to give rather large doses sufficient to produce a reaction as in some instances the patient has seemed to improve only after a reaction. A dose of a half billion may be used at first, and this may be doubled until it becomes large enough to produce some local and general reaction, after which it should be increased more cautiously. It may be necessary to run it up to eight billion. In the first 14 cases treated by vaccin seven patients died and seven recovered. These were very severe cases. In one instance, it was used because the child was so hypersensitive to serum that it could not be administered. Recovery took place. In general we would recommend it in cases that tend to run a chronic course, i.e., do not clear up after six to eight doses of serum or tend to relapse, and also in those very rare cases that show an intolerance for serum.

During the past three years we have been using a stock or preferably an autogenous vaccin intraspinally combined with serum, when such is available, in cases of meningitis not caused by the meningococcus. The purpose has been to obtain a reaction intermediate between the rather slow reaction following the subcutaneous use and the rather violent one following intravenous injection. Under this treatment (I do not claim the treatment as the cause) there has been recovery in one case of influenzal meningitis[118] and one case of staphylococcic meningitis, and in one case of B. coli meningitis the fluid became sterile, but a hydrocephalus developed nearly three months later. In several other cases a good deal of temporary improvement followed the treatment, and there seemed to be no harmful results. This has accordingly been tried in two cases of epidemic meningitis; in one, showing a complicating pneumonia, death finally resulted. In the other, in which after 12 injections of serum there was little clinical improvement and a positive culture, the patient promptly recovered after two intraspinal injections of vaccin, combined with serum. This method of administering vaccin is, therefore, I think, worth trying, when other methods have failed.

Types of Serum Reaction.—The effects of serum, apart from the curative action, may be divided into three groups:

First, in most cases the administration of serum is followed in from four to eight hours by a reaction that consists in a rise of temperature of from 1 to 3 degrees, an increase in headache and restlessness, often by pains in the legs. If this is at all severe, the pain and restlessness should be controlled by sedatives.

Secondly, serum sickness. This occurs in a varying percentage of cases, varying it is believed with the horse from which the serum is withdrawn. There is an urticarial eruption in about 8 to 12 days after the first injection. This is often accompanied by a rise in temperature, vomiting, an increase in the meningeal symptoms and intense itching. Sometimes swelling of the joints occurs. Intramuscular injections of adrenalin are of value. This is, of course, the same reaction that may follow any administration of serum. It seems to be little influenced by the quantity of serum given, and judging from the time of its appearance is caused by the first dose.

According to Ker and Rolleston[119] this reaction occurs in 60 to 75 per cent. of cases living over 10 days from the time of the first treatment. The rash may appear as late as the twenty-first day. Rolleston considers the injection of serum during the reaction to be undesirable while Ker has not observed any ill effects in doing so. We would be inclined to agree with Ker. In cases that relapse and require the administration of serum at an interval of several days after the first series of injections have been given we have on two or three occasions observed urticarial eruption appearing in from 24 to 48 hours after the serum is injected. This same accelerated reaction also occurs in diphtheria. The rash of either the usual or accelerated reaction may come out every day for several days and be accompanied by fever.

Thirdly, there may be a very severe immediate reaction to the serum. This is very rare. In only one case has there been so much sensitiveness to the serum that it was impossible to use it. In this case, each of two injections was followed by alarming symptoms of respiratory and circulatory disturbance. The serum could not be used, and vaccin was tried with good results.

In one other case the patient seemed to respond very badly to the serum though it did not take the form of an immediate and alarming reaction, but he seemed worse after each of two or three injections and improved when they were stopped. Recovery took place.

Possible Danger from Lumbar Puncture and the Administration of Serum.—The question of possible danger from lumbar puncture with or without the administration of serum is not infrequently raised. In only three instances in our experience in doing about 6000 lumbar punctures has death followed when the case was not moribund before the puncture was begun. One of these was a woman with endocarditis who was suffering from meningeal hemorrhage. She died suddenly with symptoms of pulmonary embolism during the second lumbar puncture performed on her. We have heard of another similar case, and we feel that great care should be exercised in doing lumbar punctures in cases showing bad heart lesions for the same reasons that such patients should be protected from any strain. Of course there is nothing specifically harmful in the operation of lumbar puncture. The other two instances were in children under a year of age, following lumbar puncture and the administration of serum.

One of these was a child two months old that had been severely burned by being placed in a mustard bath. The child died immediately following the third lumbar puncture; 35 c.c. of fluid had been withdrawn and 20 c.c. of serum injected. This had been the dose of serum on the two previous occasions. The child seemed to stand the puncture well, and the burns were being dressed by a member of the family when it was noticed that the child was becoming cyanotic. She was found to be pulseless, and the attempts at stimulation, artificial respiration, etc., were without results. The child in the second case was four months old. It had received an injection of serum two days before and was brought to the hospital. During the afternoon it had seemed worse, had not nursed well and had vomited. The pulse and respiration had been increasing. Thirty-five cubic centimeters of fluid was removed and about 15 c.c. of serum injected. The heart suddenly stopped beating and did not respond to energetic and immediate stimulation. As both these cases had received serum before, death could not have been due to sensitiveness to the serum. Since in both instances the quantity of serum injected was much less than the quantity of fluid removed it does not seem probable that increased intracranial pressure could have been a factor.

While the fatalities are fortunately very rare, it occasionally happens that cases go into collapse immediately following lumbar puncture and the administration of serum. This should be treated by atropin or adrenalin hypodermically, by artificial respiration, if indicated, and massage of the heart.

This condition occurred several times during the first two or three years when we were using large doses of serum. It has been very rare of late. It may follow a second or third injection, being preceded and followed by uneventful injections, and so is evidently not due to a special sensitiveness of the patient toward the serum. Kramer[62] attributed it to trikresol used as a preservative, but this has been satisfactorily disproved. It is doubtless often due to pressure, but it occurs sometimes when the amount of serum injected has not been large, no larger than at previous injections, and when a much larger quantity of fluid has been withdrawn. According to certain workers, the liberation of toxin through the destruction of the meningococcus is a possible source of danger. We have been asked on several occasions to explain the occurrence of collapse two or three hours after the serum has been administered—it being felt that the collapse was to be accounted for in some way by the action of the serum. In connection with the occurrence of collapse or death following either immediately or in two or three hours after the injection of serum, it is instructive to read this account from Ker,[104] in regard to the course of events before serum was used. "The end is often sudden, the condition of the patient changing for the worse with little or no warning, the pulse, for instance, remaining reasonably good and the respiration easy until five minutes to an hour before death. The patient collapses and in a few seconds is pulseless. He may rally for a little, if appropriate treatment is employed, but the improvement is only slight and does not, as a rule, last long. Only one of my patients survived collapse of this kind and he ultimately recovered." It is worth considering, therefore, that the collapse may be due in some cases to the progress of the disease and that the administration of serum may be only a predisposing factor in inducing the collapse at that particular time.

It must also be remembered in connection with the fatal cases that in children with an enlarged thymus or of the status-lymphaticus type, a very slight cause may be followed by serious results. Symmers[120] has shown that meningitis is often prone to be rapidly fatal in cases of status-lymphaticus.

The possibility of a lumbar puncture being a factor in causing the development of meningitis in cases of septicemia has already been discussed in the paragraph on meningism.

In view of the large number of lumbar punctures performed with safety, it does not seem reasonable to hesitate to do it, if there are indications for it, any more than to remove tonsils or adenoids or perform any other simple operation although in any of these cases there may be a fatal outcome in an unusual type of child. Especially is this so when one considers the grave risk of omitting or delaying a lumbar puncture when a child may be suffering from meningitis.

The beneficial effects of the serum, while they have been referred to more at length in preceding paragraphs, may be chiefly summarized as: (1) Reducing the mortality from 60 to 80 per cent. to about 20 to 25 per cent. (2) Reducing the average duration of the disease from three to six weeks to less than two weeks. (3) Reducing the occurrence of sequelæ from about 23.5 to 6.3 per cent. according to Netter and Debré's[2] figures.

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CHAPTER CLIX

SEPTICEMIA

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Definition.—Severe bacterial infection is always accompanied by general constitutional symptoms which result from the absorption into the circulation of toxic substances from the primary focus of disease or accompany the actual invasion of the blood stream by the infecting microörganism. In the first instance, the condition is a *toxemia,* and, in the second, a *septicemia. Bacteriemia* expresses the presence of bacteria in the blood. When the infecting organism in a bacteriemia produces multiple secondary suppurative foci, the condition is known as *pyemia.* In certain diseases such as typhoid fever and syphilis, the presence of the infecting agent in the blood is practically always found at one stage of the disease and at that time, therefore, a bacteriemia occurs. In other instances, there is a secondary invasion of the blood by organisms from a localized pyogenic infection. Septic infection or sepsis are terms sometimes used to denote septicemia or the grave symptoms such as high fever, prostration and general intoxication which accompany severe local infection by the common pyogenic bacteria.

Unfortunately there is some confusion in the use of all of these terms and no definition can be given which is universally accepted. Toxemia, for example, would be limited by some to those instances such as diphtheria in which a true bacterial toxin is concerned and not applied to the intoxication in infections by other bacteria which form no such soluble toxin. Such a restriction of the term seems somewhat pedantic. Septicemia, also, is not infrequently used in a bacteriological sense to indicate merely bacteriemia. Sepsis in the days of putrefying wounds had a literal significance which it no longer possesses. Many still employ it as a clinical term to express severe intoxication from some local phlegmonous inflammation without implying a bacteriemia, while others use sepsis and septicemia synonymously. In either case toxemia and septicemia are preferable and many favor discarding the terms "sepsis" and "septic infection" as obsolete and confusing. In view of the present-day conceptions of bacterial disease, it is somewhat more exact to call the symptoms arising from circulating poisonous products in bacterial infection toxemia; to refer to the condition in which microörganisms are present in the circulating blood as bacteriemia; and to designate a combination of toxemia and a known bacteriemia as septicemia. A toxemia is always present in bacterial infection and varies considerably in degree. It may be so severe as to simulate that of a general infection without an actual bacteriemia being present, and, while severe toxemia generally accompanies a bacteriemia, occasionally organisms may be present in the circulating blood with only slight general toxic symptoms.

Toxemia.—Two varieties of bacterial toxemia are readily distinguished. The first group which may be termed *specific toxemias* includes the limited number of infections in which a true soluble toxin (exotoxin) is absorbed from a local area. Diphtheria and tetanus are the most frequent and striking examples of this class. These very potent toxins affect particularly certain highly specialized tissues such as nerve and muscle. Similar soluble exotoxins are formed by the *B. aerogenes capsulatus* and *B. pyocyaneus*. In botulism, also, there is an absorption from the intestine of a true toxin which in this instance is not the result of infection but of the accidental introduction of the poison with food. These toxemias are characterized by rather constant symptoms and are considered elsewhere. They are enumerated here to distinguish them from a second type of bacterial toxemia which is quite distinct from that mentioned above and is the common variety found in infections. The origin of the toxic substance in this latter form of toxemia is obscure, since most microörganisms do not form definite specific toxins. It is certain, however, that in any focus of bacterial infection or even any non-infectious inflammatory area, there are formed toxic substances the absorption of which causes a fairly definite form of intoxication. This toxemia may vary in degree but the changes are so similar in infections caused by different organisms that the condition appears similar in all and the symptoms are for the most part the result of a *non-specific* toxemia.

The early theory of this form of toxemia assumed that it was due to the absorption from an inflammatory area of the products of putrefaction. It was shown experimentally that the injection of putrid material into animals was accompanied by profound toxic symptoms, and that the poisonous character of such putrid solutions was not changed by boiling which would kill all living elements. The high incidence of secondary bacterial putrefactive and proteolytic changes in any open wound or abrasion made this explanation readily acceptable. With the discovery of bacteria and the development of asepsis, however, such putrefactive changes became rare and the toxic symptoms which followed infections by organisms with little or no putrefactive action could not be interpreted on this basis. The discovery of diphtheria and tetanus toxin led to the expectation that similar specific bacterial poisons were formed by all pathogenic bacteria but it was soon shown that the production of soluble toxins is confined to relatively few organisms. Pfeiffer,[1] in working with cholera vibrios, found that the bacterial cells after being washed free from culture medium and killed were very toxic upon injection into animals. He, therefore, expressed the belief that specific intra-cellular toxic substances were liberated after the destruction of the bacterial cells. These were termed endotoxins and differ from true toxins by failing to cause the formation of antitoxins. The endotoxin conception of Pfeiffer assumed that specific poisons exist in the bacterial cells and their liberation after bacteriolysis by protective immune substances of the body results in the toxic symptoms. This view was widely accepted for a number of years but evidence has accumulated to throw so much doubt upon this conception that at present it is difficult to attribute any but a minor rôle to specific endotoxins if indeed they exist at all.

The work of Vaughan[2] first raised a doubt regarding the specificity of the toxic substances obtained from bacterial cells by showing that other proteins as well as bacteria contained toxic molecules that were liberated upon hydrolysis with alkalinized alcohol. These toxic split products had many of the pharmacological properties of the so-called endotoxins and, upon injection into animals, produced fever and other symptoms usually associated with the intoxication of bacterial infection. These observations served to explain why the bodies of non-pathogenic bacteria contain intra-cellular poisons similar to those found in pathogenic organisms. Later, Friedberger[3] and his collaborators demonstrated that toxic substances similar to Vaughan's split products are formed when bacteria of various kinds are brought in contact with normal or immune serums. These poisons have a similar pharmacological action and are formed with equal ease from pathogenic and non-pathogenic bacteria. These and other similar observations render the assumption of preformed specific endotoxins unnecessary for the explanation of the toxemia of bacterial infections, since all bacterial cells furnish non-specific toxic substances during bacteriolysis. Although certain differences in toxicity exist in extracts obtained from different bacteria, similar variations have been noted in the toxicity of split products from different non-bacterial proteins. Clinical manifestations of bacterial toxemia in different infections are characterized by differences in degree rather than by the appearance of specific symptoms in various infections.

The manner of production of the toxic substances from bacteria in infections is of some interest. Friedberger[3] believes that the bacteriolysis is brought about by the action of antibody and alexin of the serum with the formation of "anaphylotoxin" while Jobling and Petersen[4] suggest that the bacterial protein is decomposed by means of non-specific serum protease. Obviously, in local infections such intoxication arises from the destruction of organisms in a local area while in septicemia there is a widespread distribution of the bacteria which may be acted upon by proteolytic agencies.*

There is some evidence that the intoxication which accompanies bacterial infections is probably influenced also by other non-specific poisons not derived from the bacteria themselves. Jobling and

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* An excellent resumé of the subject of bacterial toxemia will be found in the chapter on "Bacterial Anaphylaxis," in Zinsser's "Infection and Resistance."

Petersen[5] have demonstrated the adsorption of anti-ferment in the blood by bacteria, thus disturbing the normal ferment-anti-ferment balance. They suggest that the excess of serum protease thus liberated may digest blood plasma and form "serotoxins" from the host's own protein. Cooke and Whipple[6] have shown experimentally that certain metabolic changes characteristic of proteose intoxication are common to bacterial infections also and that identical changes are found in sterile inflammations. They believe that proteose or other toxic digestion products absorbed from an inflammatory area are formed for the most part by the proteolysis of the body protein, and that the chief rôle of bacteria in such inflammations is to incite the inflammation by local cell injury.

In the production of bacterial toxemia, therefore, the evidence indicates that non-specific poisons resulting from proteolysis are chiefly concerned. These poisonous substances may be derived from the destruction of the infecting organism or from the tissues of the host. It is difficult to exclude the possibility of the presence of preformed specific poisonous molecules or endotoxins in certain bacteria but these, if present, probably play a secondary part in the production of toxic symptoms. Small amounts of soluble toxin also have been found under certain conditions in cultures of several organisms such as typhoid and dysentery bacilli and the cholera spirillum, but it seems quite unlikely that these exotoxins are produced in sufficient quantity to cause a true toxemia in infections by these organisms. The non-specific toxic substances probably belong to the primary products formed by proteolysis, and recovery from the toxemia due to them apparently depends upon their rapid oxidation into simpler non-toxic compounds by further ferment action rather than upon their neutralization by immune substances.

Septicemia.—The presence of bacteria in the circulating blood occurs under several conditions. Local infections with pyogenic organisms are in certain instances accompanied by the invasion of the blood stream while occasionally, the local infection is so insignificant that it cannot be detected either during life or at necropsy, such septicemias being called cryptogenetic. Certain diseases such as scarlet fever and diphtheria are not infrequently complicated by a secondary septicemia with one of the pyogenic cocci, usually a streptococcus. Typhoid fever, on the other hand, is an example of an infection in which a bacteriemia almost constantly occurs at some stage of the disease. Finally, there may be a breaking down of the protective forces of the body just before death and an agonal invasion of the blood by the infecting organism or by bacteria from the intestinal tract. The microörganisms that are most prominent in causing bacteriemia are the streptococci, the staphylococci, the pneumococci, the typhoid and tubercle bacilli. Among other bacteria less commonly found are the colon bacilli, the meningococci, the gonococci, the paratyphoid and pyocyaneus bacilli, while most of the known pathogens occasionally gain access to the blood stream.

The manner of the introduction of microörganisms into the blood may be through the rupture of an area of infection into a vein such as sometimes occurs in tuberculosis, in which a caseous bronchial lymph-node discharges its contents into a branch of the pulmonary vein with consequent bacteriemia and miliary tuberculosis. In other instances, especially seen in streptococcus skin infections, the bacteria are carried from the local inflammatory focus by means of the lymphatics and by passing through the regional lymph glands, reach the thoracic duct and thus the blood. Not infrequently an acute inflammatory area involves a neighboring vein and the infection continues through its wall. With the involvement of the intima, a thrombus forms which enlarges and furnishes a medium for the multiplication of the infecting organisms many of which are thrown off into the blood. It is by this means that a pyemia with multiple abscesses may occur if pyogenic bacteria are involved. Portions of the infected thrombus break free and those which lodge in the lung capillaries form pulmonary abscesses, while smaller bits or freed organisms passing through the pulmonary vessels lodge in the capillaries elsewhere in the body, with the formation of similar local suppurative foci. In many infections, however, in which septicemia occurs, there is no demonstrable microscopic evidence of the exact mechanism by which the organisms reach the blood. It has been mentioned that cases of cryptogenetic bacteriemia occur in which the primary local infection is so insignificant that it escapes careful search. Very frequently no recognizable difference can be found either clinically or microscopically between inflammatory foci which have initiated a septicemia and those which have remained localized. The ability of a microörganism to extend to the blood depends upon its virulence and is sometimes termed its *invasive* power. This capacity is more potent in some strains than in others, and must depend upon the ability to overcome the defensive forces of the body. It seems probable that in such cases the organisms gain access to the blood through the capillaries in the inflammatory area possibly in some manner associated with minute thrombi.

It has been shown that various bacteria may under certain conditions pass through the intestinal mucosa of a healthy individual and cause a portal bacteriemia. Some of these organisms may even be demonstrated in the systemic circulation. Such a condition is transient and these accidental invaders are soon removed. This phenomenon is suggested as the explanation of the presence of "normal" agglutinins for the colon bacillus found in the blood of normal animals. An actual infection of the blood in this manner, however, with the production of symptoms, apparently rarely occurs. Some hours after death, when the protective immune substances of the body are no longer available, a post-mortem dissemination of organisms from the intestinal tract may occur, but such diffusion of bacteria 10 or 12 hours after death must be distinguished from the "agonal" invasion of an infecting organism that takes place during the last hours of life. This terminal bacteriemia is the result of the inability of the body to keep the organisms localized or to destroy those that gain access to the blood and represents a final breaking down of the defense mechanism of the individual.

Bacteria which reach the blood stream are, as a rule, quickly removed and destroyed with little opportunity for multiplication. This removal and digestion of circulating organisms is one of the functions of the fixed cells of certain organs. The process has been studied by Wyssokowitsch[7] with the typhoid bacillus and *M. tetragenus;* by Werigo[8] with anthrax bacilli; by Filatow[9] with *B. subtilis;* by Arima[10] with staphylococcus aureus, colon and typhoid bacilli; by Kyes[11] and Bull[12] with pneumococci; by Bartlett and Ozaki[13] with staphylococcus aureus and by Hopkins and Parker[14] with hemolytic streptococci. The observations made by these various investigators have in general been in agreement. The endothelial cells of the lung, liver and spleen are especially active in this phagocytosis and the digestion of the organisms results from a slow intra-cellular enzyme action. Polymorphonuclear leukocytes in these organs may aid in the process. Other organs such as kidney, marrow, muscle and lymphatic tissues apparently play a relatively insignificant part in the removal of circulating organisms. Although this continuous destruction of bacteria takes place, there is frequently a more or less constant discharge of the bacteria into the blood so that a bacteriemia may persist for a considerable length of time, probably until an increased immunity prevents further ingress from the focus of infection. The removal or drainage of an active infectious focus by operation also is frequently followed by the disappearance of a septicemia. In some instances the discharge of bacteria into the blood is periodic, and, as these organisms are soon destroyed, temporary periods of bacteriemia alternate with intervals in which the blood is free from living bacteria. It is probably only when the infection becomes overwhelming and the defenses of the body collapse that growth and multiplication of the infecting organism takes place in the blood. When this happens death is imminent. Sometimes a so-called chronic septicemia persists for a number of months. In these cases the organisms are being more or less continuously discharged into the circulation from an infectious focus, usually from vegetations on a heart valve.

The secondary localization of bacteria during septicemia depends in part upon an apparent selection by different organisms of certain tissues that offer better conditions for their development. Such a selective action is usually assumed to be due to an inability of certain tissues to resist local implantations of these organisms during bacteriemia and this resistance is greatly diminished by any tissue trauma. A mechanical injury such as the fracture of a bone furnishes a favorable focus for the localization of circulating bacteria, and it has been suggested that the frequent localization of pyogenic cocci on a heart valve is facilitated by the possible production of a minute trauma to the valvular endothelium by the closing of the valve cusps on each other. The predilection of the staphylococcus aureus for localizing in the bones, lungs, kidneys and myocardium and of the tubercle bacillus for all tissues except striated muscle, however, does not always seem to depend upon any injury to these organs. The common localization of streptococci and pneumococci in joints during bacteriemia can apparently be explained only by a special predilection of these organisms for these tissues. A most interesting contrast in localization of different organisms in the same tissue is found in the infection of the long bones by the tubercle bacillus and the staphylococcus aureus. The tubercle bacillus becomes localized in the epiphysis of a bone and the staphylococcus with equal regularity lodges not in the epiphysis but at some point beyond the epiphyseal line. Although a secondary extension of the infection may involve the adjoining epiphysis or diaphysis, the primary point of implantation is quite constant.

One possible localization of bacteria during septicemia as a result of trauma is of special interest and concerns the danger of offering a point of localization in the meninges following lumbar puncture if organisms are present in the circulating blood. From observations made by Weed, Wegeforth, Ayer and Felton[15] in experimental septicemias in laboratory animals with *B. lactis aerogenes*, *B. pyocyaneus*, *B. paratyphosus B.*, and a strain of streptococcus, they conclude that "the intravenous injection of a sufficient number of organisms virulent within the meninges will produce a typical leptomeningitis if the cerebrospinal fluid is withdrawn during the artificial septicemia." Although the proof of a similar localization in man due to lumbar puncture during septicemia is obviously difficult to demonstrate conclusively, isolated observations render such an explanation of certain meningeal infections quite probable. The possibility of danger should be remembered in rachicentesis when septicemia is present or suspected.

When bacteria in the circulation lodge in various organs and cause the formation of abscesses, the condition is known as pyemia. Any such secondary suppurations at points distant from the initial infection are in reality part of a pyemia although secondary processes like osteomyelitis, meningitis, or arthritis are usually not so designated unless accompanied by abscesses in the viscera. It is customary to consider as pyemia only those cases in which multiple visceral or subcutaneous abscesses occur although such a restricted application of the term is not based upon any essential difference in pathological action. Secondary suppurative foci may be caused by almost any of the organisms that produce septicemia, although the multiple visceral abscesses so characteristic of the usual form of pyemia are almost always due to the staphylococcus aureus. The kidneys, lungs, myocardium and spleen are the internal organs commonly affected.

Technique of Blood Culture.—For satisfactory blood cultures the most careful aseptic technique must be observed since accidental contamination renders the detection of any blood invader difficult or impossible. The chief sources of contamination are three, the syringe, the skin of the patient and the air. The mere boiling of a syringe is not always sufficient since such heating does not destroy spores and air organisms readily adhere to the moist surfaces. Probably one of the most satisfactory methods is to enclose an all glass syringe with needle attached in a cotton stoppered glass tube and sterilize in the usual manner by dry heat. This does not injure the syringe, assures sterility and furnishes an instrument available at short notice. The skin of the patient may be prepared by washing with alcohol although mechanical cleansing with soap and water followed by a wet bichlorid dressing for a few minutes or by iodin and alcohol renders contamination from this source less likely. After obtaining the blood the needle should be removed before inoculating the culture media, and the flasks, tubes or plates opened only long enough to allow the addition of the blood.

Venous puncture in infants and children requires only slightly more technical skill than in adults but it is a common observation that many persons even after considerable experience continue inexpert in this procedure. The two most important and essential requisites for successful punctures are that the needle used is quite sharp and that the child is firmly held. In older children one of the veins at the bend of the elbow is usually available, but in infants and when the arm veins are not easily seen, the external jugular must be chosen. In the prone position with a pillow beneath the shoulders and the head rotated to one side and extended the vessel is rendered more prominent especially when the child struggles or cries. In very young or athreptic infants when the jugular vein cannot be located, the longitudinal sinus is the only available site for puncture. The hair should be shaved or clipped and the puncture made at the posterior portion of the fontanelle in the mid-line. The head must be very steadily held by an assistant. A 20-gage needle, 1½ in. in length, is the most satisfactory size for all punctures, and possesses several advantages over a smaller size. Scalp veins or small veins around the ankle while frequently of sufficient size for intravenous injection are rarely satisfactory for withdrawing blood.

In inoculating culture material it seems of some importance to dilute the blood considerably in order to lessen the inhibitory action of the serum. It is probably better to add not more than 2 or 3 per cent. of blood to culture medium for this reason, although if only a few organisms are present, their presence will not be detected unless several flasks or plates are inoculated. The cultures should be examined daily and not discarded as negative until a week has elapsed since sometimes growth appears after several days. Contaminations that may occur are the staphylococcus albus, and spore-bearing bacilli from the air. The number of organisms present can be estimated only by inoculating agar plates with definite amounts of blood. For routine cultures glucose broth or agar is most commonly used although various enriched media are indicated when the organisms suspected are difficult to cultivate.

Pathology of Toxemia, Septicemia and Pyemia.—The most important pathological changes caused by these conditions are those of a chemical and biological nature which profoundly alter the normal metabolic and functional processes of the body-cells. Although the exact mechanism of this pathology of function is not well understood, certain of these changes have been mentioned in preceding paragraphs. The morphological alterations found in the various tissues, however, appear relatively insignificant when the severity of the process is considered, and their relationship to the functional derangement is still obscure.

The anatomical changes may be divided into two groups, the first including those resulting from local injury either from primary or metastatic foci, and the second, the general alterations in gross and microscopic structure of the tissues. No detailed description of the local inflammatory foci accompanying septicemia is necessary since they present no special characteristics. They may be of the exudative type in pyogenic infections or of the proliferative type in miliary tuberculosis or typhoid fever. In some cases, especially with streptococcus infections, the primary focus shows an apparently insignificant amount of inflammatory reaction and in cryptogenetic septicemias the primary lesion may be so slight as to escape discovery. In the production of pyemic abscesses, it has been shown experimentally that in normal animals such multiple foci develop much more readily when the organisms (staphylococci) are injected into the circulation together with small inert particles. These cause various *loci minoris resistentiae* by plugging the smaller vessels and thus the circulating bacteria more easily gain a foothold. Some difficulty is experienced in securing anatomical evidence that a similar mechanism always exists in the production of metastatic pyemic foci in man. In cases of endocarditis or of phlebothrombosis, the origin of multiple infected emboli is apparent, but the majority of cases of staphylococcus pyemia in children originate from acute osteomyelitis or skin suppurations in which the anatomical demonstration of possible sources for emboli is difficult. It may be that certain circulatory changes in toxemia render possible the production of multiple metastatic foci that would not occur in a normal animal. Petechiæ or larger ecchymotic extravasations may be found under the skin, serous and mucous membranes or in the organs and are frequently regarded as the result of minute infected emboli in these locations, especially since they are more common in cases of endocarditis and pyemia. The demonstration of a bacterial origin in such hemorrhagic foci, however, is difficult.

The general anatomical alterations in the tissues from toxemia and septicemia are for the most part similar and differ in degree more than in the production of characteristic changes by specific organisms. Although the specific toxins of diphtheria and tetanus cause certain more or less distinctive lesions, those found in most infections are probably the result of non-specific intoxication. The exact part played by the organisms themselves aside from definite local inflammatory foci is difficult to estimate. The severity of the general changes parallels as a rule the degree and duration of the intoxication.

The most commonly observed lesions are in the parenchymatous organs in which moderate toxemias are accompanied by a diffuse cloudy swelling of the cells, and more severe grades of intoxication by a fatty infiltration in addition. The liver, kidneys and myocardium show these alterations most characteristically. Small scattered focal areas of necrosis may also accompany severe toxemia. These are found in the liver especially in typhoid fever, and also occur in the pancreas and in the lymphoid follicles of the spleen and lymph-nodes. Unless the necroses are very recent a few polymorphonuclear leukocytes may be found in and around them but the absence of organisms indicates that such areas are not due to bacterial localization. In the same organs an increase of interstitial tissue which sometimes follows certain infections points to a more extensive necrosis. The spleen in septicemia is swollen and the pulp has a soft semi-diffluent consistency which leaves a velvety opaque reddish-gray cut surface after incision, the so-called acute splenic tumor. The swelling is due chiefly to a marked hyperplasia of pulp cells although the malphighian bodies in many instances are also enlarged and prominent. Certain toxemias as, for example, that of scarlet fever and less frequently those due to known organisms such as streptococci and pneumococci incite both proliferative and exudative lesions in the renal glomeruli, possibly from the effect of toxic substances during the process of excretion.

The blood being one of the most accessible organs has been more extensively studied during life, and those changes which are usually most striking occur in the formed elements, although chemical alterations also are present. One of the most characteristic changes is the anemia which accompanies severe toxemia and septicemia. The degree varies with the severity and duration of the process and the red cells may be diminished to half the normal number of even less, with a corresponding reduction in hemoglobin. A relative and absolute increase in polymorphonuclear leukocytes is fairly constant in those toxemias and septicemias in which exudative changes occur, especially those due to pyogenic organisms. In the infections in which proliferative changes predominate as, for example, tuberculosis and typhoid fever, such leukocytosis is usually absent unless there is also a mixed or secondary pyogenic infection. As a rule the increase in leukocytes during septicemia is quite definite and occasionally reaches 80,000, especially with streptococcus infections, although usually the count is less than half this figure. In some cases no increase occurs and this is of grave prognostic significance since it indicates an inability on the part of the patient to react to the infection. The chemical changes in the blood in toxemia and septicemia that have been recognized are relatively few. There is usually an increase in non-protein nitrogen[6] which is easily demonstrable and which is probably associated with the general increase in protein metabolism. Severe grades of toxemia in animals with proteose intoxication are also accompanied by a marked decrease in the blood plasma. Not infrequently an acidosis occurs in severe infections with diminution in the alkali reserve of the blood.

This acidosis is due to the presence of B-oxybutyric and aceto-acetic acids, to lactic or possibly other acids, and is apparently explained by a temporary failure to metabolize and excrete these acid bodies. At necropsy the blood from cases of septicemia has a greatly diminished coagulating power.

Symptoms.—The severity of the general reaction is usually proportional to the toxemia and varies within wide limits. In mild infections the symptoms may consist only of slight general malaise and fever while severe toxemias are accompanied by marked prostration or other indications of severe functional changes. The symptoms of septicemia are due to the associated toxemia and are characterized only by being especially severe. Only general symptoms will be mentioned since special signs due to primary or metastatic infectious foci are usually those of local disease.

In infants with milder grades of toxemia, the usual symptoms are moderate fever with general restlessness and irritability which tend to interfere with sleep. Frequently, gastro-intestinal disturbances such as anorexia, vomiting, and diarrhea occur especially in the artificially fed. In more severe infections the fever may be high and one or more convulsions at the onset are not unusual. The temperature reaction is subject to considerable variation. A fever of 102 to 105°F. is the rule and marked fluctuations may occur. The regular remissions characteristic of septicemia in adults are unusual in infancy although they may be noted in later childhood. Not infrequently a hyperpyrexia of 106°F. or above is noted at some time during the course, more often in streptococcus and pneumococcus infections. In other cases there may be little or no fever or even a subnormal temperature especially in weak infants with poor circulation. A sudden rise in temperature which in adults is frequently accompanied by a chill may be shown in infancy by a convulsion. Rigors also occur and are characterized in infants more by stiffness and moderate cyanosis than by a shaking chill. Evidences of increased pressure of the cerebrospinal fluid such as a bulging fontanelle, neck rigidity and positive Kernig's sign may be noted during a toxemia without demonstrable infection of the spinal fluid. This meningismus is presumably due to a meningeal irritation and is usually transient. With toxemia, a continued loss in weight occurs and a definite athrepsia may develop or, especially when vomiting and diarrhea persist, an anhydremia. Such severe nutritional disturbances are more common in severe toxemia and septicemia. Stupor, coma, and circulatory collapse are terminal manifestations.

Older children present similar differences in symptoms corresponding to the severity of the toxemia. In mild cases there may be only slight general symptoms such as headache, anorexia, lassitude and slight fever. When the onset is sudden it may be accompanied by vomiting. With increasing toxemia there is a rather high irregular fever with full, rapid pulse and marked weakness. The urine contains albumin and is scanty and concentrated unless there is an increased fluid intake. Occasionally there is a toxic anuria. The appearance of acidosis is indicated by an increased pulmonary ventilation. Irritability and restlessness may be replaced by delirium as the prostration continues, or the patient may sink into a semi-stupor from which he is aroused with difficulty. Petechiæ or ecchymotic blotches may appear in the skin. The so-called typhoid state, in which the chief symptoms are moderately high fever with periods of quiet stupor alternating with wide-eyed restlessness, a low delirium, incoherent mutterings and picking at the bed clothes, occurs not only in typhoid fever but also in many of the eruptive fevers, erysipelas, influenza, acute miliary tuberculosis, pneumonia, etc. Pulmonary edema, cardiac irregularity, cyanosis, falling temperature and coma commonly terminate the illness.

Septicemia from Various Microörganisms.—The majority of instances of septicemia are due to the pyogenic cocci especially the streptococci, the pneumococci, and the staphylococcus aureus. In order to illustrate the relative incidence of septicemia with these organisms, I have tabulated the cases observed during the past five years at the St. Louis Children's Hospital. These include only those children in whom positive cultures were obtained from the blood either during life or at necropsy since in other instances in which the clinical picture indicated a septicemia, the identity of the infecting organism was uncertain.

Relative Incidence of Septicemia with Pyogenic Cocci in Children

	Number	Cases of pneumonia
Hemolytic streptococci—alone	48	32
Hemolytic streptococci—with staphylococcus aureus	3	2
Non-hemolytic streptococci—alone	7	2
Non-hemolytic streptococci—with staphylococcus aureus	2	1
Staphylococcus aureus—alone	28	10
Pneumococcus—alone	16	14
Total	104	61

These patients were all under 11 years of age, approximately half being infants in the first two years of life. From a review of the clinical course and the pathological findings an attempt was made to determine the focus from which the septicemia developed. The proportion of these cases in which the apparent portal of entry of the organism was the lung has been tabulated and the relatively high incidence of such a primary focus is quite apparent, especially with hemolytic streptococci. In 29 instances a temperature of 106°F. or above was recorded. Such hyperpyrexia occurred in about one-third of the streptococcus and pneumococcus infections but in only one-fifth of those due to staphylococcus aureus. In 12 cases the temperature was 107°F. or above, three being over 108°F. and one 109°F.

Streptococcus.—Septicemias caused by the streptococcus are probably the most frequently encountered as well as the most dreaded of all general infections. They are usually accompanied by profound toxemia and in most cases are fatal. In recent years it has become customary to separate these organisms into two groups by the property of producing hemolysis in vitro which is possessed by certain strains and to speak of hemolytic and non-hemolytic streptococci. The organisms so frequently found in severe infections and septicemias belong to the hemolytic group, and, while it is known that certain non-pathogenic strains are hemolytic, hemolytic activity has been considered an indication of pathogenicity in organisms isolated from human infections. In general, it has been customary to consider that these hemolytic streptococci of human origin belong to a single type and to speak of "the" hemolytic streptococcus. It has recently been shown, however, by Dochez, Avery and Lancefield[16] that it is possible to distinguish several distinct types of hemolytic streptococci by immunological reactions, and that these types do not change antigenically after animal passage. Tunnicliff,[17] also, has found the hemolytic streptococci from scarlet fever cases immunologically distinct from organisms from other sources, and a similar immunological identity in strains isolated from erysipelas. In septicemia, no attempt has been made to differentiate the strains isolated, and while these organisms may all belong to a single type, it seems more likely that several types possess such invasive power.

The most frequent portal of entry of hemolytic streptococci is through the lungs where the organisms are especially prone to cause a bronchopneumonia. Although in some cases this pneumonia may be primary in a previously healthy child it is much more common that hemolytic streptococci gain entrance during some other disease and a so-called secondary infection of the lung results. Such secondary bronchopneumonias are somewhat more frequently found in those infectious diseases accompanied by a catarrhal inflammation of the bronchi especially influenza, measles and pertussis, which apparently lower the normal resistance to the entry of streptococci and other organisms. Many of the cases of so-called primary pneumonia are preceded by a bronchitis so that even in these instances the streptococci may be secondarily implanted during a period of lowered local resistance. Other infectious diseases, or nutritional disorders in infants, also are not infrequently complicated by similar pulmonary infection. The source of the infecting organism in these instances is through contact infection in the majority of cases, either from a healthy carrier or from proximity to another case of respiratory infection with hemolytic streptococci. Another group of cases of secondary streptococcus bronchopneumonia may be considered auto-infectious since inflammatory foci are present in the upper respiratory tract and organisms pass to the lungs by an extension of the process. These include the bronchopneumonias complicating otitis media, mastoiditis, paranasal sinusitis, and pharyngeal inflammations due to streptococci. A third and much less common source of secondary pneumonia is that due to the lodgment in the lung of organisms during a septicemia from some more or less distant focus of infection. The importance of these secondary streptococcus pneumonias lies in the frequency with which they are accompanied by a severe toxemia and also by an invasion of the blood stream by the infecting organism. Both the epidemiology and the incidence of septicemia in these cases have been studied in outbreaks of measles[18] and of influenza[19,20,21] during the past few years in Base Hospitals of the American Army, and in these studies the importance of the hemolytic streptococci has been greatly emphasized. Sufficient observations have been made to demonstrate that similar streptococcus pulmonary infection with septicemia is also of frequent occurrence in children. In such pneumonias streptococci are only rarely found in the circulating blood during the early stages of the disease since any organisms reaching the blood stream are rapidly removed by the normal defense mechanism of the patient. When this resistance is overcome, however, by severe infection, many organisms reach the circulation and may be demonstrated by blood culture. After such a collapse of the body defenses and consequent overwhelming of the blood with bacteria, death is almost certain and such septicemia is frequently called "terminal." Usually blood cultures are negative during the course of the disease and the organisms may be grown from the blood only during the last days of life or at necropsy. In the rare instances in which recovery has taken place after the demonstration of hemolytic streptococci in the blood, it is probable that the culture was taken at a moment of transient bacteriemia in an individual whose resistance was sufficient to oppose successfully the invasive power of the streptococcus since, fortunately, all cases of streptococcus pneumonia are not accompanied by a terminal septicemia.

In addition to the pulmonic portal for hemolytic streptococcus septicemia, almost any local streptococcus infection may furnish the initial focus from which a general infection develops. Among the more common of such local infections are erysipelas and infections following burns, wounds or other abrasions of the skin, while those cases folowing severe pharyngeal infections as for example in scarlet fever, and complicating a peritonitis are not unusual. The extension of an otitis media and mastoiditis to thrombosis of the laterial sinus, meningitis, and septicemia may also be mentioned as a not infrequent sequence in children. An enumeration of the various local inflammations from which a streptococcus septicemia has resulted would include all possible primary streptococcus inflammations. Cryptogenetic septicemias in which the primary focus remains hidden even after a careful search at necropsy are more frequently encountered with hymolytic streptococcus infections than those due to other organisms. It is possible that in some of these cases, the portal of entry may have been the intestinal tract. All hemolytic streptococcus septicemias with only occasional exceptions are characterized by being terminal, and are accompanied by an extremely severe toxemia. In certain infections, however, a few organisms occasionally reach the blood stream and may lodge at some distant point with the production of secondary suppurative foci. The localization of organisms in this transient form of septicemia is most commonly in one or more joints with the production of a purulent arthritis. Meningitis, pleuritis, peritonitis, endocarditis, pericarditis, subcutaneous abscesses and other localizations may also occur. Recovery may take place in this transient septicemia if the infection can be localized, although a terminal septicemia may follow from the extension of one of the metastatic suppurations.

The non-hemolytic streptococci, also, probably include a group of more or less distinct strains, which at present have not been clearly differentiated. The streptococcus viridans, a strain producing greenish colonies on blood agar, has been isolated from the blood and cardiac vegetations in cases of endocarditis, while similar organisms, some of them failing to produce a green pigmentation, have been found in chorea, rheumatic fever, and other conditions. In general the non-hemolytic streptococci are less virulent than the hemolytic strains, and in cases of endocarditis[22] cause a chronic septicemia in which the organisms can be grown from the blood more or less constantly over a period of months. In addition, non-hemolytic streptococci sometimes terminally invade the blood stream under conditions somewhat similar to those mentioned in connection with hemolytic varieties as, for example, in pulmonary infection such as bronchopneumonia or empyema, peritonitis, otitis, infected wounds, etc.

In a group of 60 patients with streptococcus septicemia observed in children at the St. Louis Children's Hospital, 51 were due to the hemolytic and nine to non-hemolytic strains. In 34 of the former and three of the latter a bronchopneumonia was the focus from which the blood infection occurred. Six of the hemolytic streptococcus septicemias were cryptogenetic and three followed erysipelas while all the other cases arose from variously located primary infections. In only one instance in this series did recovery follow the isolation of hemolytic streptococcus from the blood. This was a mild case of scarlet fever. In certain other instances secondary suppurative arthritis due to a streptococcus was observed frequently with recovery, although these cases were not included because positive blood cultures were not obtained. In 18 of the 60 cases inflammatory lesions in the joints, meninges, endocardium, pericardium, or peritoneum were present as a result of secondary metastatic localization of the organisms.

Staphylococcus.—Although local infections and especially those of the skin by the staphylococci are quite common, the proportion of such local processes that become generalized is relatively small. Considering all septicemias that occur in children, however, those due to staphylococci predominate even over those due to streptococci on account of the number of relatively mild septicemias which are caused by the former organism. The staphylococcus aureus is by far the most virulent and commonly observed member of this group found in septicemia, while in comparatively few instances does the staphylococcus albus invade the blood and still less frequently is the staphylococcus citreus found. The primary focus of infection which forms the portal of entry for a staphylococcemia may be located in various places. In addition to skin lesions such as furuncle or carbuncle, secondarily infected burns or other trauma, some of the more common initial foci are tonsillitis, otitis, paranasal sinusitis, pyelitis, pneumonia or pleuritis. Infection of the umbilical cord in newborn infants occasionally also may be the primary site.

Although all septicemias may occur with varying degrees of severity under different conditions, it is with staphylococcus septicemias that these different forms are most readily illustrated. They may be divided into three groups:

1. Mild, or transient septicemias in which a few organisms reach the circulation and localize at some point of lowered resistance. A characteristic example of this type is the so-called "primary" acute osteomyelitis which is almost exclusively due to staphylococci and which must obviously result from a transient septicemia. The localization of these organisms in the bone marrow is relatively common in children and is confined almost entirely to this period of life. In adults, the affection is rare and practically all cases occur before the third decade, i.e., during the growth period of bone. The staphylococcus has a predilection for this tissue which is rather remarkable when compared with other organisms. In occasional instances, other bacteria such as streptococci, pneumococci, and tubercle bacilli may localize in the diaphyses of bones during a septicemia, but the majority of cases of acute osteomyelitis due to organisms other than staphylococci result from direct extension as, for example, in osteomyelitis of the mandible from alveolar infection or that following a compound fracture. Other metastatic localizations in these temporary staphylococcus septicemias occasionally occur and may result in an acute arthritis, or more rarely in an abscess in the brain, peri-renal tissues or in some other location. The origin of the septicemia in these cases and especially in acute osteomyelitis is frequently obscure since only occasionally is any other suppurative focus of staphylococcus infection demonstrable so that most instances are classed as cryptogenetic. Any explanation of their source is speculative although their entrance through the upper respiratory or the alimentary tract seems somewhat more probable than through the skin. From the incidence of acute osteomyelitis it would seem that living staphylococci are present not infrequently in the blood of apparently healthy children. It is usually stated that the great vascularity of the growing bone and the budding arrangement of the finer vessels and capillaries mechanically favor the deposition of organisms in the metaphysis, although such purely mechanical factors might be expected to favor other organisms equally well. Certainly, circulating staphylococci have a special tissue

predilection for the metaphyses of the long bones. The not infrequent history of trauma to the bone preceding the inflammation indicates that such localization may be favored by injury.

A subacute or chronic form of septicemia sometimes occurs in which metastatic foci, usually in bone, develop at intervals over a considerable period of time. This chronic form is seen usually in the course of a chronic osteomyelitis and may be considered as a recurrent transient septicemia. The incidence of staphylococci in such temporary septicemias as illustrated by acute osteomyelitis is shown by an analysis of a series of cases from the St. Louis Children's Hospital. In 42 consecutive cases in which the infecting organism was identified, the staphylococcus aureus occured 37 times, the staphylococcus albus three times and the tubercle bacillus and a streptococcus once each.

2. Severe or pyemic septicemias, in which the organisms are present in the blood in larger numbers and multiple secondary suppurative foci develop. Although any metastatic suppuration such as acute osteomyelitis, acute arthritis, etc., may properly be called pyemia, it is to those cases in which multiple abscesses form in the internal organs that the term is most commonly applied. In rare instances staphylococcus pyemia may be cryptogenetic in origin but most cases develop from some well-defined local infection, such as a furuncle or an acute osteomyelitis. A phlebitis from the direct extension of a suppurative focus may also initiate a pyemia and here embolic pulmonary abscesses are common. Any staphylococcus infection is a potential starting point for pyemia although skin and bone foci are those which most frequently precede general involvement. The clinical course is short and characterized by symptoms of severe toxemia with high fever, marked prostration, leukocytosis, delirium, and coma. Since staphylococci are readily grown from the blood, confirmation of the diagnosis in pyemia is easily obtained. The secondary abscesses develop with most constancy in the myocardium and kidneys but do not as a rule cause any characteristic clinical signs. An acute pericarditis secondary to mycardial infection may occasionally be recognized. Other common netastatic purulent foci occur in the lungs frequently accompanied by pleuritis, in the spleen, bone marrow, subcutaneous tissues, and less often in the voluntary muscles. One localization of special interest is a vegetative endocarditis. These cases are relatively rare in children except as part of a severe pyemia but occasionally occur in early life. They are rapidly fatal and accompanied by infected infarcts of the viscera, and not infrequently also by a pustular skin eruption, probably the result of mycotic emboli.

3. Terminal septicemias, in which the blood invasion from the primary focus occurs as an agonal event. These septicemias are similar in character to terminal infection from streptococci and may follow bronchopneumonia, less often peritonitis, skin phlegmons, etc., due to the staphylococcus aureus. In adults it is only in occasional instances that staphylococci pass into the blood from cases of bronchopneumonia, even terminally, but in staphylococcus pneumonias in

children, on the other hand, the organisms are found rather frequently in the blood at necropsy. The time which elapses between the blood invasion and death is apparently too short in these cases for the production of secondary suppurative foci.

The staphylococcus aureus was demonstrated in the blood either during life or at necropsy in 30 cases of pyemia and terminal septicemia from the St. Louis Children's Hospital during the past few years. Of the 16 instances of pyemia eight complicated acute osteomyelitis, six arose from skin infections and the other two from sinus phlebitis. A hemolytic streptococcus was present as a terminal invader in three cases. Terminal staphylococcus septicemias occurred 14 times usually from a secondary bronchopneumonia following influenza, measles, otitis media or nutritional disorders. Twice a severe peritonitis, once an otitis media and once furunculosis were apparently the primary foci of infection.

Pneumococcus.—The demonstration of organisms in the blood in lobar pneumonia in adults has varied somewhat with different observers. A rather large series carefully studied in this respect at the Hospital of the Rockefeller Instiute[23] showed septicemia in 30 per cent. of the cases during life, with a much higher mortality than in those patients with negative blood cultures. Types I and II of the pneumococcus were more prevalent in this group than Types III and IV. A series of 70 cases of croupous pneumonia in children[24] showed pneumococci in the blood during life in only 13 per cent. The pneumonias in infants and children are more frequently of the lobular variety and more commonly caused by Type IV pneumococci[25,26,27] than by the so-called fixed strains, if organisms isolated from the sputum can be taken as an indication of the strain infecting the lung. Results based upon this method must be accepted with some caution, however, on account of the considerable percentage of individuals in whom Type IV is normally present. No data exist upon which to base any conclusions as to the incidence of septicemia in pneumococcus pneumonia in children especially with reference to the different strains. Invasion of the blood stream undoubtedly occurs in some instances during the course of the infection and a terminal septicemia in a certain proportion of cases is shown by post-mortem bacteriological observations. In many cases, however, cultures of the blood taken at necropsy are sterile when pneumococci are found in the lungs. Certainly the isolation of pneumococci from the blood during life in children is of grave prognostic import.

In addition to those instances in which septicemia follows pulmonary infection, other primary portals of entry exist, of which the middle ear is the most frequent. Here, a sinus phlebitis, brain abscess or meningitis is usually associated with the otitis. Severe pharyngeal or tonsillar inflammations, appendicits, paranasal sinusitis, cholecystitis or enteritis due to a pneumococcus may also be followed by septicemia. Other primary foci are usual, although cryptogenetic infections are not infrequent.

Secondary metastatic localizations of pneumococci when they occur either from pulmonic or other foci or associated with cryptogenetic septicemia are found chiefly in three locations, the endocardium, the meninges and the joints. The *endocarditis* may be the vegetative or the malignant ulcerative type and has no distinctive characteristics either clinically or pathologically. Even after the organisms have localized on the heart valves, positive blood cultures are obtained in only about one-third of the cases so that confirmative evidence of the lesion cannot always be obtained in this manner. This contrasts sharply with instances of sinus phlebitis in which the organisms are present in the circulating blood with more or less constancy. Such septicemic lesions as chorio-retinitis, or panophthalmitis, and isolated abscesses which are occasionally noted are usually embolic in origin. Pneumococcus *meningitis* is characterized by a rapidly fatal course and a terminal septicemia in which the organisms frequently are present in the blood in large numbers. The *arthritis*[28, 29] is commonly mono-articular and as a rule the larger joints are involved especially the knee and shoulder. No articulation, however, is exempt. The onset is sudden with pain and swelling of the joint. The synovial exudate may be serious, fibrinous, or purulent and resembles that occurring in pneumococcus inflammation of the pleura. Of the less frequent localizations of the pneumococcus, peritonitis[30] and osteoperiostitis[28] are occasionally observed. Pleuritis and pericarditis, while sometimes a result of septicemia are usually produced by direct extension from pulmonary lesions.

In a group of 16 infants and children with terminal pneumococcus septicemia 14 originated from pneumonia which was primary in eight instances. Only two were lobar pneumonia. In nine cases the type of pneumococcus from the blood was determined and found to be Type IV in five, Type III in two and Type II in two. One of the Type II septicemias originated from an otitis media and the other from a sphenoidal sinusitis, these being the only instances in which the primary infection was not a pneumonia. The relatively high incidence of Type IV pneumococcus in this series supports the assumption made from sputum examinations that pneumonia in infants and children is more often due to members of this heterogenous group than to one of the fixed types.

B. Coli.—Whether or not the members of the colon group* of bacteria cause septicemia except in rare instances has been the subject of much discussion. They have been found not infrequently at necropsy both in the blood and in the other organs but many of such cases have shown little or nothing in the clinical course of the illness to suggest a septicemia. In other cases pyogenic bacteria as well as colon bacilli were present in the blood. In the large proportion of such instances the dissemination of intestinal bacteria was probably agonal or post-mortem. The fact previously mentioned that normally a few intestinal organisms may occasionally be carried into the portal circulation renders such dissemination somewhat more frequent with members of this group. However, undoubted instances of true colon septicemia have been observed both in adults and children although such blood infections occur with greater frequency in the newly born and in young infants than in older children. Nothing characteristic in the clinical picture serves to differentiate a septicemia due to colon bacilli from other septicemia and it is only by the isolation of the organisms from the blood that a diagnosis may be made. Frequently no local suppurative focus accompanies the infection and the lesions found at necropsy are those of toxemia sometimes with ecchymoses of the serous membranes. In such cases the intestinal tract is believed to be the portal of entry, an assumption possibly favored by the frequency of alimentary disturbances in young infants. The occasional instances of meningitis due to the colon bacillus give evidence of a blood infection. The organisms may gain entrance through the umbilical wound in the newborn while a pyelitis which sometimes accompanies the septicemia suggests that the portal of entry may be the urinary tract.

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* The organisms of this group have minor fermentative differences with certain sugars, but no certain pathogenic distinctions have been shown to be characteristic of various strains. Usually, an exact classification of the organism isolated has not been attempted so that the designation *B. coli* included *B. communis*, *B. communior*, *B. acidi lactici*, *B.* (*lactis*) *aerogenes*, *B. cloacae*, *B. neopolitanus*, *B. coscoroba*, and possibly other varieties sometimes differentiated by bacteriologists. The organisms of the *B. mucosus capsulatus* group which includes the pneumobacillus of Friedlander, are closely related to the colon group and the conditions under which they are found in the blood are similar although the former are somewhat less frequently encountered.

It is certain that while septicemia with colon bacilli does occur in a certain number of instances, it is much less common than post-mortem bacteriological findings indicate. This is shown by an analysis of 22 records of infants under one year of age from the St. Louis Children's Hospital. In all of these cases colon bacilli were isolated from the blood at necropsy, and both the clinical and postmortem records were carefully studied for evidence of septicemia. In 10 of these there was no clinical or morphological evidence of a septicemia and respiratory or digestive lesions offered sufficient explanation for death, while in three other instances pyogenic cocci were also present in the blood. Three cases had a severe general peritonitis and in these the invasion may have been terminal. Five others had a severe pyelocystitis but in only two of these was there an obvious septicemia, an extensive purpuric eruption in one and multiple abscesses in the other. One infant four days old had multiple visceral hemorrhages possibly due to a septicemia from umbilical infection although no gross lesion was apparent. Of these 22 cases, therefore, only six had any demonstrable evidence of severe infection, aside from the growth of the organism from the blood, and in three of these the septicemia was probably a terminal one. The difficulty in interpretation of the occurrence of the organisms in the heart's blood at necropsy is thus illustrated.

Gonococcus.—Although gonococcus infections usually remain localized, an invasion of the blood occurs in certain instances. The presence of gonococci in the exudate of arthritis cases complicating gonorrhea, first noted by Petrone[31] in 1883, was convincing evidence that gonococci must have been present in the blood at some period before the arthritis. It was not until 1894, however, that Hewes[32] found the organisms in blood cultures in this complication. Since then gonococci have been grown from the blood in a number of instances of gonorrheal endocarditis.[33] The relatively infrequent demonstration of the organisms in the blood is probably due in part to the difficulty in their cultivation as compared with most bacteria, and in part to their sporadic and transient presence in small number in the circulation.

In the gonorrheal infections in infants and children, on the other hand, there has been little bacteriological investigation of the blood although Hunner and Harris[34] have found gonococci in blood culture in a 14 year old girl with bilateral pyosalpinx and peritonitis of gonorrheal origin and Marfan and Debre[35] report a similar case with positive blood culture in a girl 10½ years old with chronic gonococcus vulvovaginitis who developed pelvic peritonitis and later endocarditis, pericarditis and pleuritis. Dwyer[36] has observed an acute gonorrheal endocarditis in an infant 23 months old with vaginitis, arthritis, and a subcutaneous abscess in the lumbar region. Gonococci were grown from blood culture and were demonstrated in smears from the vaginal discharge, from the abscess and from the valvular vegetations at necropsy. Cases of arthritis complicating gonorrheal vulvovaginitis have been not infrequently observed, Hartley[37] in 1887, reporting the first gonorrheal vaginitis cases in which the organisms were demonstrated also in the joint exudate. Others[38, 39, 40, 41, 42,] have confirmed the presence of gonococci in the joint fluid of arthritis, cases associated with gonorrheal vaginitis, although the complication is not especially common. Hamilton[43] has collected from the literature reports of more than 1900 cases of gonorrheal vulvovaginitis in children from three days to 12 years of age most of which were confirmed bacteriologically. In this group 35 cases of arthritis occurred but no mention is made of other complications referable to a bacteriemia.

From an ophthalmia neonatorum also the gonococcus may cause septicemia with arthritis, and in such cases the infection is not infrequently fatal. Clement Lucas[44] in 1899 collected from the literature 23 cases of this nature, the earliest reports having been made by him in 1885. In some of these cases gonococci were found in the conjunctival exudate, and although bacteriological examination was lacking in most of these infants, the clinical evidence indicates that all were probably cases of gonorrheal arthritis. Other observers[46, 47, 48] have identified the organisms in the joint lesions as gonococci. Brehmer[49] noted this complication in an infant with gonorrheal ophthalmia dying on the seventh day and Reinhard[50] reports a case of gonorrheal urethritis with development of epididymitis and arthritis in an infant with death at one month of age. Other metastatic infectious foci may result from a gonococcemia as, for example,[51] a four year old girl with gonorrheal vaginitis who developed a tenosynovitis of the wrist in which gonococci were found: or that reported[52] of an 11 year old girl with vaginitis, polyarthritis and pleuritis in which gonococci were present in smears and cultures from the pleural exudate. A number of cases of arthritis in which gonococci were found in the aspirated joint fluids both in smears and in cultures but in which there was no demonstrable portal of entry for the organisms have been described by Kimball[53] and by Holt.[54] The children were 18 boys, from one month to three years old, who had no other evidence of gonococcus infection. The cases occurred during one or more epidemics of gonorrheal vaginitis in the hospital, and the authors believe that infection was transmitted by nurses in cleansing the patients' mouths. Many of the children affected had severe thrush but in none could gonococci be found in cultures from the mouth, nose, eyes or urethra.

Gonorrheal septicemia then is evidenced in children by an arthritis which may complicate a gonorrheal vulvovaginitis or ophthalmia. Exposed children may develop bacteriemic arthritis without evidence of a local infection. It is possible also that septicemia may occur from a gonorrheal infection of the umbilical cord although the predilection of the gonococcus for serous and mucous surfaces, and the absence of any convincing evidence of infection in this manner make such a portal of entry somewhat unlikely.

Although secondary metastatic processes occur in gonococcus septicemia, it must not be assumed that all suppurative lesions noted during gonococcus infection are due to this organism alone. Indeed, secondary infection by other pyogenic cocci readily occurs in this disease particularly in the more severe cases. In the case reported by Hunner and Harris[34] in which a gonococcemia was demonstrated during life, at necropsy the blood showed a streptococcus and this organism also was associated with the gonococcus in the peritoneal exudate. Similarly, Finger[48] notes that while the gonococcus alone was found during life in the knee joint of a child with arthritis from ophthalmia neonatorum, the post-mortem examination showed the streptococcus in addition in this joint while in another joint the latter organism only was present. Joint complications that occur with vulvovaginitis during the course of a scarlet fever may be too readily attributed to the gonococcus without bacteriological confirmation. The reported bacteriology of fatal gonococcus infections is relatively meager, but there is evidence that many of the fatal cases succumb to a secondary septicemia from one of the pyogenic cocci, usually a streptococcus. The secondary invader may gain entrance through the original portal of entry of the gonococcus—a so-called mixed infection—but frequently comes through a different channel, the usual lesion being a streptococcus pneumonia with septicemia.

A question of particular interest in connection with gonococcus septicemia in children is the possibility of the existence of several strains of the organism some of which have a tendency to be more virulent than others. In the majority of cases of vaginitis in children the infection, while of a chronic nature, is very benign in character, without constitutional effect, and with no serious complication. It is rare that an ophthalmia is acquired from this source, although the vaginitis may become widely disseminated in a hospital ward. Ophthalmia neonatorum, on the other hand, is more frequently a serious infection and resembles more nearly the type of inflammation seen in adult forms of gonorrhea. In this connection the observations of Pearce[55] are significant. She studied six strains of gonococci from vulvovaginitis cases, nine from acute urethritis in adults, and three from ophthalmias, one of the latter from an infant, by means of agglutination and complement fixation tests on monovalent immune rabbit serums made from each of the various strains. By these immunological reactions the organisms fell into two distinct groups, the adult strains being indistinguishable from the ophthalmia organisms and the strains from these two sources clearly separate from those isolated from the vulvovaginitis cases. These differences in the two groups are, of course, only relative but striking enough to suggest the possibility of such differences being associated with a corresponding variation in virulence. More recently Hermanies[56] also has determined by agglutination and absorption tests on a large number of strains that the gonococci are composed of a number of distinct immunological types which have little relation to one another, although two of these types included over 90 per cent. of the strains studied.

The pathology of gonococcus septicemia is not essentially different from that due to other pyogenic cocci. The joint lesions are typical of acute arthritis and consist of a congestion of the synovial membrane, which is thickened and infiltrated with inflammatory products. The adjoining cartilage and ligaments are also more or less implicated in the process.

Clinically, the general symptoms of gonococcemia observed are not as a rule especially striking. The temperature is usually irregular and only moderately elevated ranging from 100 to 103°F. with occasionally higher temperatures as successive joints are involved. A leukocytosis of 20,000 or more is common, and there may be albuminuria. Young infants show relatively more prostration and severe grades of athrepsia are frequently observed as the disease progresses. The non-specific toxemia due to the local inflammatory process renders a clinical recognition of septicemia difficult since the intoxication alone may simulate a general infection. A diagnosis can be made only by bacteriological examination of the blood or by the development of arthritis. The local symptoms of joint involvement consist of a rapidly developing articular swelling with redness and acute tenderness, and may appear very soon after the infection is acquired. Sometimes the symptoms gradually subside without the development of an effusion, but in many cases fluctuation appears, usually at the end of the first week. The aspirated fluid is yellowish, thin, slightly turbid, and may coagulate rapidly. Rarely is thick pus obtained.

Microscopic examination shows a preponderance of polymorphonuclear cells with extra-cellular and intra-cellular gonococci. Occasionally, especially in early exudates, the organisms are difficult to demonstrate microscopically, but may be grown on suitable culture media. The arthritis is polyarticular in a large majority of cases, usually four or five joints being affected. Any articulation may be a point of localization although spondylitis is difficult of recognition in younger children. The smaller joints of the hand, foot, wrist and ankle are probably more often involved, with the knee, shoulder and elbow somewhat less frequently. The sternoclavicular, temporomaxillary, sacro-iliac, and intraspinal joints which are not infrequently affected in adults are rarely involved in children. Skin eruptions, also, which have been noted in general gonococcus infections in adults as either erythematous, ecchymotic, petechial or maculopapular rashes, are rare in similar childhood infections although pustular and vesicular eruptions complicating gonorrheal ophthalmia in infants have been described.[57] In the absence of severe nutritional disorders and secondary infections convalescence is usually prompt. Better results are obtained by aspirating fluctuating joints or by incision if the exudate is purulent. A resultant ankylosis is unusual.

Meningococcus.—Although in both the sporadic and epidemic forms of meningococcus infection the incidence in children has greatly exceeded that in adults, most of the observations on meningococcemia have been made in the latter. This is due in part to the fact that cultures have been made less often in children and in part to the unusual opportunity of observing epidemics both in America and in Europe in army camp hospitals during the World War.

The various phases of cerebrospinal fever including septicemia have been reviewed in detail by Rolleston[58] in light of these recent observations. It seems quite likely that a transient invasion of the blood stream by meningococci precedes most if not all of the cases of meningococcus meningitis. Herrick[59] states that this early premeningitic stage was recognized in 45 per cent. of 265 cases and that with a special technique positive blood cultures can be obtained in from 50 to 80 per cent. of patients at this early period, while Baeslack[60] reports 36 per cent. of positive blood cultures in these cases. Such early bacteriemias are usually only recognized in hospitals during epidemics for obvious reasons. A positive blood culture may be followed by a negative one after a short interval of five hours.[61] In occasional instances the septicemia may exist for some weeks or even months before the appearance of meningitis[62, 63, 64] and positive blood cultures have been obtained during the course of acute meningeal infection as well as in some cases after the acute meningitis has subsided.[65]

In addition to this early transient premeningitis bacteriemia,[61] septicemia without meningitis occurs sporadically and especially during epidemics.[66] Occasionally, abortive forms of meningococcemia are recognized in which the blood infection is overcome relatively rapidly. Certain cases of purpuric eruptions with fever but without meningeal symptoms observed during epidemics probably are of this type. Sainton and Maille[67] have described a case with a maculopapular rash, synovitis of two joints and fever but no meningeal signs. The entire course of the illness occupied only a few days and meningococci were found in the blood and synovial fluid from both joints.

Another group of such cases includes the dramatic fulminating forms which are fatal within 48 hours or less from their onset. The intoxication symptoms appear suddenly and are of extreme severity with intense headache, vomiting and collapse. A purpuric eruption frequently with large spreading hemorrhagic blotches is characteristic. Hemorrhages also occur in the mucous and serous membranes. The temperature may be slightly elevated but is not constantly so probably as a result of the collapse. Death supervenes before any exudate is demonstrable in the meninges. This form is thought to be less often seen in infants and children than in adults. A third group of cases without meningitis may be called subacute or chronic meningococcemia, in which the organisms persist for weeks or months without the development of meningitis. Here the disease may take the form of a continued or intermittent fever, which Netter[68] first described as pseudomalarial and pseudotyphoid forms. The disease may be accompanied by chills, fever and sweating with moderately enlarged spleen. Various forms of erythematous and papular rashes or petechiæ are usually noted although the infection may occur without any skin manifestations.[69, 70, 71] In exceptional instances the meningococcemia may persist for three or four months.[72, 73]

The localization of meningococci during the septicemia is of especial interest and in many instances such localized lesions give conclusive evidence of meningococcemia. Aside from meningitis, the skin lesions are the most frequent in occurrence and are present in 35 per cent.[59] and 59 per cent.[58] of two reported series of cases. The organisms have been cultivated from the skin lesions in some instances and it seems probable that some if not all the rashes are due to a skin localization of the organisms. Although erythematous, macular and papular rashes occur, the most characteristic rash is hemorrhagic. The larger purpuric blotches are seen typically in the fulminating cases and have a graver prognostic significance than the more frequent smaller petechiæ. Vesicles or bullæ from which meningococci have been grown in pure culture may form over the hemorrhagic areas.

Localization of organisms in the synovial membranes occurs not infrequently. The first demonstration of meningococcemia by blood culture was made by Gwyn[74] in a case of meningitis with arthritis. In 1727 cases of meningococcus infection collected from several sources by Rolleston, the incidence of arthritis was 6 per cent. although it is less common in infants and children than in adults. The clinical types of joint lesions are somewhat varied[75] but the most common form is an acute suppurative arthritis, which is characterized by a moderate swelling with slight redness and local heat. While in some cases the joints are very painful, as a rule functional impairment is slight and movements well tolerated. In many instances the lesion is transient and several joints may be slightly affected for a few days, while in the more severe cases a single joint, usually the knee, is the seat of the inflammation. The affection resembles in many respects the arthritis of gonococcemia. The effusion is at first a rather thin, turbid, serous exudate frequently with a grass-green tint, and shows many polymorphonuclear leukocytes and meningococci. The organisms are readily cultivated on suitable media. If the effusion persists, the purulent character becomes more pronounced and flakes of fibrin appear. The prognosis is good and most cases clear up rapidly without special treatment. If the effusion persists aspiration should be done. The intra-articular injection of anti-meningococcus serum has been apparently beneficial,[59] although this is rarely necessary. A permanently impaired function from ankylosis has been observed but is extremely rare.

Acute vegatative endocarditis with meningococcemia, first noted by Warfield and Walker,[76] have been recognized occasionally[77, 78] and purulent inflammations of the pleura, pericardium and peritoneum due to the meningococcus are also rare complications of septicemia. One rather striking and not uncommon localization of the organisms in adults is in the epididymis or testis and the meningococcus has been obtained by puncture of the inflammatory focus.[79] In 922 cases collected by Rolleston,[58] such a localization occurred in 4.9 per cent. although the incidence varied considerably in different epidemics. It is usually transient, subsides without suppuration and is not followed by atrophy. A panophthalmitis has been noted in a few instances but there is some doubt whether this condition is of hemic origin.

The intravenous injection of anti-meningococcus serum has been used during the septicemia[59, 80] with success. It seems necessary to give considerable quantities of the serum, 50 c.c. or more being injected slowly. This may be repeated several times at 12 hour intervals if necessary. When meningitis is present, spinal drainage and intraspinal injections of serum are also given. Herrick reports the most striking results in the severe cases, in which there was often a rapid recession of symptoms. No bad effects follow such large intravenous injections of serum.

B. Typhosus and B. Paratyphosus.—Typhoid fever is one of the diseases in which a septicemia is most constantly found. Since early adult life is the period at which greatest incidence occurs, most of the observations have been made in adults, but similar studies on infants and children show that the blood infection accompanies the disease with equal constancy in the young. It has been shown that typhoid bacilli can be isolated from the blood at some time in every case of typhoid fever, most frequently during the first week. The earlier in the disease the blood is examined, the more frequently the organisms are found, since in only about half the cases do they persist during the second and in a much smaller proportion during the third week.

In a few instances they may be present later than this time. A relapse is accompanied by a renewal of the septicemia. The length of time that the bacilli remain in the blood is probably dependent upon several factors and varies with the severity of the infection, being influenced by the individual's power of resistance and by the degree of virulence of the infecting strain. It is possible that there may be some multiplication of the organisms in the blood stream but, for the most part, the septicemia depends upon the entrance into the circulation of bacilli from the many foci of infection in the lymphatic tissues. As soon as the defensive processes of the body become sufficiently potent, the further entrance of organisms into the blood stream is prevented and the septicemia ceases. The number of bacilli in the blood may vary considerably in different cases or with the progress of the disease. Frequently the blood is rich in organisms but in some cases only one of several flasks inoculated will show a growth. There seems little relation, however, between the severity of the attack and the number of organisms in the blood, although the persistence of septicemia after the second week is usually noted in only the more severe cases. As a diagnostic aid, the septicemia is of considerable importance on account of its constant and early appearance. A diagnosis is possible from blood cultures some days before agglutinins are demonstrable by the Widal reaction.

The effect of the presence of the bacilli in the blood upon the clinical symptoms is somewhat uncertain. Undoubtedly many of the organisms are destroyed and toxic bacteriolytic protein substances liberated. It is reasonable to suppose also that there is an absorption of bacterial and tissue disintegration products from the intestinal and other lymphatic tissues in addition to the introduction of living bacilli from these sources. Many of the symptoms of typhoid fever are quite similar to those produced by non-specific protein toxins and such substances are probably intimately concerned in producing the clinical symptoms noted in the disease. Whether the typhoid bacillus in the blood plays any rôle other than furnishing toxic split products after its lysis is difficult to determine. If any specific typhoid toxin occurs, its effect is completely obscured by the effect of non-specific toxemia.

In children, the occurrence of typhoid septicemia has not been the subject of such extensive investigation as in adults probably on account of the lower incidence of the disease, but the organism has been isolated from the blood in many instances so that one is justified in assuming as constant a bacteriemia in the disease in children as in adults. Doubless many cases in infants are unrecognized although occasional positive blood cultures have been reported during life.[81] The infection at this age is more often a septicemia with relatively insignificant local lesions. The transmission of the infection to the fetus through the placenta has been established by a number of reports.[83] In all such cases a septicemia occurs with a tendency to visceral hemorrhages. The placenta shows no lesion. Frequently, the infant dies *in utero;* if born prematurely or even at term, the infection is fatal within a few days. Maternal typhoid fever, however, is not always transmitted to the fetus and infection may occur after birth.

Infections with *B. paratyphosus* are quite analogous to typhoid fever with respect to the presence of organisms in the blood. Most of the reported cases in Europe have been due to the "B" type which resembles the *B. enteritidis* of Gaertner. In America the "A" type is more commonly found. Rathery[84] among French soldiers during 1914–1916 isolated the "B" organisms from the blood in 314 out of 1088 cases. I have found the "A" type in blood culture not infrequently both during the early stage of the disease and also during a relapse. Positive blood cultures have been noted in infancy[81] and also in the newborn.[85] One of the localizations of the paratyphoid bacillus that has been occasionally observed in infants is in the meninges where a suppurative meningitis may occur. Similar suppurative processes in other locations are somewhat more common in paratyphoid than in typhoid septicemia, although an osteitis due to the typhoid bacillus occasionally occurs.

Mixed septicemia in typhoid infection is sometimes observed but usually as a terminal event. Streptococcus, pneumococcus, colon bacillus or staphylococcus aureus are the secondary parasites usually found. Simultaneous infection with typhoid and paratyphoid bacilli occurs and a miliary tuberculosis may complicate typhoid septicemia.

B. Tuberculosis.—Two distinct types of bacteriemia with tubercle bacilli exist. In one, a few organisms reach the circulation from some local focus and after lodgment in some more or less distant spot incite a secondary tuberculous lesion. Probably the most common localization of such metastatic infection is the epiphysis of bone although the meninges, liver, spleen, kidney, brain and other tissues are not infrequently affected. Such lesions often heal completely without clinical manifestations and are discovered by chance at necropsy, but their occurrence is sufficient proof of a previous temporary bacteriemia. The manner of access of the organisms to the blood in these cases may be from lymph-node to lymph-node and thence to one of the larger lymphatic trunks which empty into the thoracic duct or possibly by the erosion of a capillary in a tuberculous area. Sometimes a small shower of tubercle bacilli may reach the blood in such a manner with slightly wider distribution. It is in the miliary form of tuberculosis, however, that the severe type of blood infection is found, which more closely resembles septicemia with other bacteria, and which is accompanied by profound intoxication. This form of infection is due to the entrance of a considerable number of tubercle bacilli into the blood at approximately the same time and although it is often possible in adults and in older children to demonstrate at necropsy a caseous focus which has ruptured into a vein or a lesion of the thoracic duct, such anatomical confirmation is rare in younger children. Frequently, the primary focus of infection in such cases is the bronchial lymph-nodes and it is possible that the difficulty lies in the small size of the structures involved. However, since there is less protection against the spread of tuberculous infection in younger children, the organisms may under certain conditions pass in large numbers from a focus in a lymph-node through the regular lymphatic channels to the thoracic duct. A terminal septicemia from secondary infection with pyogenic organisms is much less common in children with tuberculosis than in adults, although in severe grades of infection a bronchopneumonia with terminal septicemia from the streptococcus, pneumococcus or staphylococcus may occur.

B. Pyocyaneus.—While the bacillus pyocyaneus is of relatively slight pathogenicity in adults, it may be particularly virulent in children and especially in infants. General infection occurs occasionally and is usually fatal. Although hemorrhages may accompany any septicemia, this association is more constant in pyocyaneus infections in which there is a special tendency for hemorrhages to occur in the skin, mucous membranes and lungs. The organism may cause a general infection apparently from any primary focus, more frequently in infants from the intestinal tract or from the middle ear. In the newborn the portal of entry may be the umbilicus, as in the cases of purulent umbilical thrombo-arteritis studied by Wassermann.[86] In most of these infants there were metastatic foci of hemorrhagic pneumonia with necrosis and abscess formation. Sporadic cases of acute entero-colitis, as well as small epidemics[87, 88] in which *B. pyocyaneus* was isolated from the stools, have led to the belief that this organism may be the etiologic factor in the intestinal inflammatory process. Cases of pyocyaneus septicemia have been described[89, 90, 91] in infants with enteritis and no other demonstrable primary suppurative focus, while the presence of the organism in the stools makes it probable that the intestinal canal was the portal of entry. Septicemias following otitis media and sinusitis have been observed[91, 92, 93] and pyocyaneus infection of the skin has been the portal of entry for a general infection.[94, 95] In septicemias with the streptococcus, staphylococcus and typhoid bacillus, *B. pyocyaneus* has occasionally been encountered post-mortem probably from an agonal invasion. A toxin, "pyocyanolysin," has been described.[96, 97]

The localization of *B. pyocyaneus* during the bacteremia is in general similar to that found with other pyogenic organisms. Endocarditis[98] occasionally occurs and this lesion has been produced experimentally in rabbits.[99] Arthritis and meningitis have been described[100, 101] as well as pulmonary abscesses, although as a rule multiple purulent foci in the kidney, spleen and myocardium are not found. The most characteristic localization and one rather frequently encountered is in the skin. The presence of multiple hemorrhagic foci in infants with pyocyaneus bacteriemia[93, 102] may be due to a local accumulation of organisms but in a number of other cases the bacilli have been isolated from the skin lesions. These may take the form of papules,[103] vesicles,[104] pustules[89] or a combination of these lesions. Fraenkel[91] has described hemorrhagic bullæ, and others[106, 90] have observed cases of gangrenous ecthyma in pyocyaneus septicemia.

Several of the cases of recognized pyocyaneus septicemia have occurred in infants with hereditary syphilis, possibly due to a general lowering of resistance in such infants. The following instance recently observed at the St. Louis Children's Hospital illustrates this association of the two infections as well as some of the characteristic lesions.

An athreptic infant four months of age and weighing 3600 gm., who had been fed on sweetened condensed milk exclusively for the past month, was admitted on the fourth day of an acute illness characterized by fever, anorexia, vomiting and numerous watery stools. There was an acidosis and well-marked dehydration but no inflammatory foci were noted with the exception of a few small vesicles and pustules over the trunk. The anhydremia and acidosis improved slightly with the introduction of fluid and alkali, but the infant remained feeble and toxic, refusing all feedings and vomiting when gavaged. The stools were four daily and contained mucus but no blood. The leukocytes were 16,000 and the temperature ranged from 100 to 103°F. The Wassermann reaction was strongly positive. On the seventh day of illness, small petechial hemorrhages on the skin were noted. Death occurred on this day. At necropsy an acute entero-colitis with superficial ulceration, an acute fibrino-purulent peritonitis and pericarditis were found. *B. pyocyaneus* was grown in pure culture from the acute purulent exudate and was also isolated from the intestinal mucosa.

In general the clinical features of pyocyaneus septicemia are similar to those of other infections. The intoxication is severe and accompanied by a rather high fever which may be of a remittent type. A marked prostration with nervous manifestations such as restlessness, delirium and coma is frequently noted, while in both infants and older children diarrhea is a common symptom. In some cases the condition may simulate typhoid fever on account of the severe toxic symptoms, fever, and a slightly enlarged spleen. The course may extend over one or two weeks. There is no specific treatment.

B. Diphtheriæ.—Septicemia occurs in diphtheria not infrequently from secondary streptococcus infection and much less often from the staphylococcus aureus. The diphtheria bacillus invades the blood stream only in exceptional instances during life. In a certain proportion of cases, however, there is an agonal spreading of the organism so that at necropsy positive cultures can be obtained from the blood in about 4 to 5.7 per cent. of cases and in much higher proportion from the liver and spleen.[107, 108] Here, also, pyogenic cocci are usually present.

The absence of any inflammatory lesion in the organs from which the bacteria are isolated together with the fact that the diphtheria bacillus can rarely be obtained in blood culture during life indicate that such dissemination is terminal. The toxic symptoms in diphtheria are due almost exclusively to the absorption of the specific diphtheria toxin from the area of local infection, but may be greatly augmented by secondary infection with pyogenic cocci.

B. Influenzæ.—It is only in exceptional instances that the Pfeiffer bacillus reaches the blood stream and then usually as a terminal event.

In influenzal meningitis a septicemia occurs with some constancy[109] but in epidemic influenza the organism has been recovered during life or at necropsy in a relatively small proportion of cases.

B. Dysenteriæ.—The various types of *B. dysenteriae* do not cause septicemia. In rare instances organisms have been isolated from the liver or spleen at necropsy, but such a finding is quite exceptional. The severe toxemia that accompanies the infection is due to absorption of toxic substances from the intestinal mucosa. The Shiga organism is said to form a true toxin although this view is not universally accepted.

B. aerogenes capsulatus is not a cause of septicemia in infants and children. In rare cases a severe lacerated wound infection with the gas bacillus may be followed by a bacteriemia demonstrable during life, but except from some extensive phlegmonous lesion, any dissemination of this organism found at necropsy is a post-mortem one.

M. tetragenus and **B. proteus** have been found in the blood in a few instances but usually with other organisms and their pathogenicity is doubtful, although cases of septicemia have been described in adults[110] due to the first named organism.

In infections with **B. anthracis, B. mallei, B. pestis,** and certain other organisms, septicemia occurs but the extreme rarity of these diseases makes their consideration unnecessary here.

S. Pallida.—The dissemination of the *spirocheta pallida* by means of the blood stream in syphilis during the secondary stage is clearly indicated by the distribution of the lesions. The demonstration of the organisms in the blood in acquired syphilis has been made by Valente[111] who obtained successful rabbit inoculations in both the primary and secondary stages, although no spirochetes could be found in the blood of these cases by microscopic examination. Ulenhuth and Mulzer[112] also found that the blood from cases of early syphilis would infect rabbits although in latent and tertiary syphilis their inoculation experiments were unsuccessful. Recently, Brown and Pearce[113] in the study of experimental syphilis in rabbits have shown that the organisms pass to the blood and lymphatics within 48 hours after the primary testicular inoculation, and are widely distributed in the body before the initial lesion can be detected. The wide spread dissemination of the organisms in the organs of infants with hereditary syphilis and the ease with which they can be demonstrated in all lesions leave little doubt of a general blood distribution. It seems very likely that spirochetes are present in the blood of early infantile syphilis although their actual demonstration has not been reported. The late lesions of childhood may be due to the lighting up of a focus of organisms which have remained latent since their deposition in early infancy or during intrauterine life. However, the question of septicemia in syphilis after the secondary stage is still in some dispute. The fact that a mother with latent syphilis transmits the infection with considerable regularity to the fetus indicates that the spirochetes are present in the maternal circulation at some period during pregnancy.

The assumption of a direct extension of infection from latent uterine foci in these cases lacks probability since attempts to demonstrate such lesions have been unsuccessful. It is of interest in this connection that Graves[114] has reported successful rabbit inoculation with blood from cases of paresis. Hereditary syphilis is essentially the same process as the acquired form and if septicemia occurs in the late stages of the latter there can be no doubt that a similar condition exists in childhood.

The Infectious Exanthemata.—Although the etiological agent is unknown in measles, scarlet fever, variola, varicella, and rubella, the clinical course and distribution of the lesions indicate that the virus in each instance is distributed by the blood. In these diseases also, therefore, it seems probable that a condition analogous to septicemia occurs. It is the septicemia which results from secondary infection of the respiratory tract, however, that is of especially grave significance in these diseases and this secondary infection is most frequently due to hemolytic streptococci.

Mixed Septicemias.—Some of the various combinations of organisms which may be found simultaneously as blood parasites have already been mentioned. Usually such a condition is due to a terminal invasion by a streptococcus or one of the other common secondary invaders during an existing septicemia. Many examples might be quoted. Such mixed septicemias are not often recognized during life. At necropsy, it is usually possible to distinguish the primary parasite without difficulty by a study of the associated lesions. A septicemia from three organisms occurs occasionally as, for example, in typhoid fever complicated by a miliary tuberculosis with terminal streptococcus invasion.

Septicemia in the Newborn.—The relative lack of resistance to bacterial invasion in the newly born and during the first weeks of life greatly increases the danger of any local infection becoming generalized. Although streptococci and staphylococci are the most frequent etiological agents in such septicemias, almost all other pyogenic organisms are found more often than in later childhood. The greater susceptibility to infection and to septicemia in young infants is probably closely associated with the imperfectly developed power of the young individual to produce antibodies to bacterial infection. It has been shown, for example, in the case of complement-fixing antibodies in tuberculosis[115] and in influenza[116] that such antibodies are very much less frequently present in infants than in older children. In general the portals of entry for organisms are the same in early infancy as in later life with possibly an increased tendency for invasion from the gastro-intestinal tract in young infants. Most important, however, is the special susceptibility to infection through the umbilical cord, to which the majority of the septicemias of the newly born are due. The transmission of bacteria to the fetus during a maternal septicemia occurs in a certain small number of instances but a more common form of infection is the placental bacteriemia described by

Slemons[117] who has demonstrated streptococci in the fetal side of the placenta in such cases. This complication occurs during a prolonged labor when the membranes rupture prematurely and repeated vaginal examinations are made. Since the bacteria enter by way of the amniotic membrane the infection is more liable to be serious for the infant than for the mother. A certain proportion of these infants do not succumb immediately and probably form a distinct group of the septicemias of the newborn. It is likely that many of these have been considered cryptogenetic, since in such instances there is no localized infection of the umbilical stump. The majority of septicemias in newborn infants, however, originate in local infections acquired during or shortly after birth and particularly through infection of the umbilical cord from lack of care in dressing the stump. Here, it is usually possible to demonstrate the presence of an infectious umbilical arteritis or phlebitis accompanied in some cases by purulent omphalitis although the absence of a gross lesion does not exclude umbilical infection. Occasionally no portal of entry for the septicemia is demonstrable. The foci of localization in various organs depend somewhat on the infecting organism and do not differ materially from those occurring in later infancy. Frequently no definite metastatic inflammatory foci are found. A rather characteristic phenomenon in septicemia of the newborn is a tendency to hemorrhages which may occur as petechiæ on the skin or on the mucous or serous surfaces or, in some cases, larger ecchymoses or extravasations in these locations.

Evidence of the infection appears within 10 days of birth and is usually conspicuous. Although there may be some variation in the severity of the septicemia depending on the organism involved and the degree of the infection, in general the symptoms are those of a toxemia and differ relatively little from such conditions in later infancy. A most constant symptom is asthenia and rapid loss of weight due in part to diarrhea and in part to anorexia, although the infection itself is also a considerable factor. The infant looks ill and may be dull and apathetic, or may give evidence of nervous hyperexcitability such as hyperesthesia, irritability with a constant feeble cry, tremor or muscular twitchings and occasionally convulsions. The skin may show the ecchymotic areas previously mentioned, and icterus, which at times is severe, is frequently noted. Fever is usually present at the onset and shows considerable fluctuation. At times, particularly in severe infections when symptoms of collapse occur, the temperature is subnormal. A similar irregularity is observed in the leukocyte count which, although usually high, may sometimes fail to give an indication of infection. A moderate enlargement of the spleen is often present. The occurrence of secondary metastatic infections, of which peritonitis is the most frequent, may aid in the diagnosis but the lack of demonstrable physical signs from internal foci is notorious. In some instances septicemia in the newborn is accompanied by such insignificant clinical manifestations that the discovery of the infection at necropsy is entirely unexpected.

Prophylaxis and Treatment.—In addition to general precautions for the prevention of infections, two specific measures may be mentioned which are of much importance. First, the early recognition and surgical treatment of local suppurative processes before septic infection occurs. Delay in the drainage of an acute osteomyelitis, for example, greatly increases the danger of septicemia, and the same risk attends neglected mastoiditis or other pent suppurations. The second prophylactic measure concerns the prevention of secondary respiratory infection by pyogenic cocci in acute infectious diseases. Many diseases common in children such as measles, pertussis, influenza and diphtheria render the respiratory tract especially susceptible to a secondary invasion by hemolytic streptococci, pneumococci and staphylococci, which not infrequently results in fatal septicemia. Such secondary infections are preventable by proper isolation. Since pyogenic pulmonary infection is acquired from some human source, a strict isolation of the patient serves not only to prevent the transmission of the specific virus to others but reduces to a minimum the danger of transfer of pyogenic cocci to the patient from outside sources. Even children suffering from the same specific disease should be isolated from each other when presenting evidence of any secondary infection. In addition to the more commonly recognized transmissible diseases, children with bronchopneumonia or other open suppurative lesions, particularly those caused by hemolytic streptococci and by pneumococci, are a constant and not always appreciated source of contagion to contacts in a hospital ward and the danger of cross infection especially in infants is minimized by their isolation.

The treatment of toxemia and septicemia includes the care of local lesions as well as the general management of the infection. Primary and metastatic infections may require drainage or other procedures which are of a surgical nature and are described elsewhere. This local treatment may be of the greatest urgency and importance in certain cases where the infectious foci are accessible.

Unfortunately the use of immune serums is limited to relatively few infections. The specific toxemias of diphtheria and tetanus and their treatment by antitoxins are considered in other sections, while in only two of the diseases in which septicemia occurs have effective therapeutic serums been developed. The intravenous injections of considerable amounts of polyvalent anti-meningococcus serum in the treatment of meningococcus septicemia has already been mentioned. Its use is of special value in severe cases and in those recognized early before localization in the meninges has taken place.

In pneumococcus infections due to Type I only has an anti-serum[16] of any therapeutic potency been produced, so that specific treatment is available only in infections with this type. For this reason the infecting strain must be identified before the use of serum is justified. The so-called "mouse" method is the best for determining the type. Intravenous injections of from 50 to 100 c.c. may be given slowly at eight hour intervals to Type I infections until the symptoms are ameliorated. It has been found that such injections sterilize the blood. Its value in children, however, is limited on account of the difficulty in obtaining sputum for isolation of the organism and also because Type I infections are apparently less frequently encountered.

Anti-streptococcus serums have been employed in a variety of streptococcus infections, and, although some reports have been favorable, in general the results have been disappointing. The explanation of the unfavorable results probably lies in the specificity of the different strains of streptococci. The classification and methods for identification of the various types of pathogenic streptococci are not yet satisfactory and until they can be made so, reliable specific antiserums will not be available for use in streptococcus infections. Even in the so-called polyvalent serums the presence of specific antibodies for the types of streptococci which are commonly encountered is uncertain.

The use of vaccins and non-specific protein therapy, while of some value in certain local and chronic infections, is not to be recommended in the treatment of septicemias. When toxic symptoms are pronounced or when an acute septicemia is obviously present there is certainly no indication for supplementing the already abundant antigen or non-specific toxin in the body. In mild or subacute septicemias in which the infecting organism has been identified, no serious objection can be raised to a cautious use of autogenous vaccin although the value of such treatment is not yet certain. The indiscriminate use of commercial stock vaccins or mixtures of bacterial products, however, is a stigma of immunologic and therapeutic ignorance.

One measure which is possibly regarded as related to specific therapy and which has been rather extensively employed in the treatment of septicemia is transfusion. Although temporary improvement may follow this procedure, the majority of observers are agreed that no permanent relief is obtained and that its use is not to be recommended. It seems probable that the transient benefit observed is due rather to the improvement in the blood volume and circulation than to any antibacterial action.

The general management of toxemia and septicemia consists chiefly in nursing care and in the treatment of symptoms as they arise. The nutrition should be preserved and it should be remembered that during infections the metabolism is considerably increased and more food is needed. For higher temperatures, hydrotherapy should be employed rather than antipyretics. An ice-bag frequently relieves severe headache or delirium in older children. The so-called stimulants such as camphor, caffeine and strychnine when indicated may be given in full doses although their value is questionable. Probably the most important general measure is the preservation of the water balance in all cases of toxemia and septicemia. It is usually considered that the free use of fluids in toxemias serves chiefly to aid the elimination of toxic substances by a process of dilution and increased excretion. There is some evidence, however, that additional factors may furnish a more urgent need for fluid. In experimental toxemias[6] a well-marked diuresis is present while the tendency to desiccation during infections in infants is well recognized. The marked concentration of the blood observed at necropsy as well as the shock-like collapse which not infrequently complicates severe grades of toxemia indicate that the blood volume is seriously depleted in such conditions. The essential factors that underlie loss of liquid from the blood are not always understood but the obvious indication is to restore the blood volume by a replacement of fluid. It seems likely that the effect of transfusion is attributable to such a restoration of circulating medium. In all infections the necessity for supplying fluid constantly should be remembered. Water should be given by mouth at frequent intervals when possible. In some cases the use of physiological salt solution subcutaneously or, in infants, intra-peritoneally may be necessary, while in older children the rectal drip method may be employed. Intraperitoneal injections should be avoided, however, in those instances in which septicemia exists on account of the danger of the trauma causing a point of localization for the circulating organisms. Intravenous glucose solutions (10 per cent.) have a definitely beneficial effect in severe toxemia. Hypertonic solutions also (15 to 20 per cent.) are of undoubted value in relieving pulmonary edema.

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CHAPTER CLX

GENERAL ANESTHESIA

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Modern History of Anesthesia.—Crowford Williamson Long M.D., University of Pennsylvania 1839, a country practitioner of Jefferson County, Georgia, administered ether Mar. 30, 1842, and removed a tumor from the neck of James W. Venable, while he was under the influence of this agent. A second operation was done in July of the same year and a third in September 1843, and a fourth in January, 1845. The fact of these ether administrations and operations was only known by Doctor Long's immediate circle of friends. It was not till some years later, when rival claims were being contested, that he published the results of his own work and through affidavits from people upon whom he had operated substantiated his claims. On Dec. 10, 1844, Horace Wells, a dentist in Hartford, Conn., while witnessing a popular stage exhibition, observed one of the performers, a Mr. Cooley, who had inhaled "laughing gas" (nitrous oxid), sustain a severe injury of the leg without the least evidence of pain. In conversation with the man after the close of the exhibition he assured Wells that he did not know when he was hurt. Wells then determined to test the efficiency of nitrous oxid in his dental work. He himself inhaled the gas and had one of his molar teeth extracted while under the influence and declared that "it did not hurt more than the prick of a pin" and predicted "a new era in tooth pulling." After using nitrous oxid with considerable success in his dental practice he became convinced of the importance of his discovery and gave a public demonstration in Harvard Medical School. The demonstration was only partially successful, probably due to impure gas, a defective apparatus used for its administration or the incidence of excitement. Wells repeated his demonstration privately to a number of students that night with considerable success. While uncertain in its action "laughing gas" anesthesia became sufficiently popular to be advertised for extractions in Hartford papers. Wells investigated the relative merits of nitrous oxid and ether for surgical procedures for some years. In Hartford, Conn., a monument was erected to Wells which bears the following inscription: "Horace Wells who first discovered anesthesia, Dec. 10, 1844." A breast amputation was the first surgical operation performed under nitrous oxid. It was done by Doctor Bigelow, April, 1848, in the Massachusetts General Hospital, Boston, and "about

60 gal. of gas as a substitute for ether" (Bigelow) was used. In 1867, Colton, a New York dentist, reported 20,000 successful nitrous oxid administrations for extractions. E. Andrews, M.D., of Chicago, in 1867, suggested the employment of oxygen with nitrous oxid. Since that time nitrous oxid and oxygen have been used in combination as an anesthetic with ever increasing success.

William T. G. Morton was associated with Wells in his dental work in Boston during 1842 and 1843 and was familiar with Wells' employment of nitrous oxid as an anesthetic but considered it unreliable. At this period the plates of artificial teeth were worn over the stumps and roots of decayed teeth. Morton felt that he could make better fitting plates if all the stumps and roots were removed but he had difficulty, on account of the pain, in persuading patients to submit to the necessary extractions. Morton had studied chemistry, especially in its relation to the ingredients required for the manufacture of artificial teeth, with Jackson, who was perhaps the most renowned chemist of the day, and in his desire to find an anesthetic agent that was always reliable and safe he consulted Jackson, who suggested ether. Morton administered ether to animals till he was satisfied that it could be depended upon to produce unconsciousness and that it was safe, and after inhaling it himself to the stage of unconsciousness he administered it on Sept. 30, 1846, to a man suffering with an ulcerated tooth which he extracted without pain. After administering it to several patients successfully, Morton applied to John Collins Warren, who was the founder and chief surgeon of the Massachusetts General Hospital, for the privilege of demonstrating a new anesthetic agent which he called "Letheon." The privilege was granted and on Oct. 17, 1846, Morton administered ether and Warren operated. At the close of the operation Warren, who was a very conservative man, holding the scalpel aloft, in a most dramatic manner exclaimed to the large audience of medical men, students and laymen present, "Gentlemen this is no humbug," Morton's efforts to disguise the odor of ether by the addition of essential oils was fruitless as Doctor Bigelow, an associate in surgery with Doctor Warren, detected the nature of the agent. Bigelow immediately sent the news to London and Paris and in a remarkably short time ether was being used throughout the civilized world as an anesthetic. December 19, 1847, Dr. James Simpson, Prof. of Midwifery in the University of Edinburgh and physician-accoucher to the Queen of Scotland, first employed ether during a forceps delivery and a few days later for the pains of ordinary labor.

Chloroform.—On Mar. 6, 1847, Flourens announced to the Academie des Sciences* that chloroform exerted an anesthetic effect on the lower animals analogous to that of ether. On Nov. 10, 1847, Dr. James Simpson read a paper entitled "Notice of New Anesthetic Agent as a Substitute for Ether in Surgery and Midwifery" before the Medico-Chirurgical Society of Edinburgh. The "New Anesthetic

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* Comptes Rend., xxix (1847), p. 342.

Agent" was chloroform and Simpson reported having used it successfully in 50 administrations. Because of the more agreeable odor and greater ease of administration chloroform for a time largely displaced ether, with the notable exception of the northeastern part of the United States where confidence in ether has never been lost. It was thought that chloroform was as safe as ether but a death on Jan. 28, 1847, less than three months after its introduction, which was soon followed by reports of others from every quarter of the globe dispelled this illusion. As death after death occurred it became evident that whatever advantage chloroform might have it was by no means free from grave risks to life. In 1847 Flourens also directed attention to the anesthetic properties of ethyl chlorid and in the following year Heyfelder first administered the vapor for operation. Although Heyfelder's administration was successful, ethyl chlorid was not recognized to any extent as a general anesthetic agent till 1895.

Respiration, Anoxemia.—One of the foremost responsibilities of the anesthetist during the maintenance of anesthesia is to recognize and eliminate all the factors which tend to produce even slight degrees of anoxemia. A higher level of safety to the patient will be attained if an adequate amount of oxygen gains access to the system throughout the narcosis because the respiratory center in the medulla is depressed by an anoxemia, particularly if it is sufficient to produce cyanosis, either in the acute form or by a gradual process. Not only is the respiratory center depressed if the blood is in a condition of anoxemia but cardiac dilatation and paralysis are much more apt to occur if the coronary vessels which nourish the heart are filled with venous blood. Except in pure gas anesthesia, convulsions or clonic muscular movements are rare and are not to be expected during an asphyxial death when ether or chloroform is being administered. Muscular rigidity, when accompanied by cyanosis, calls for more oxygen and less of the anesthetic.

The Effects of General Anesthetics on the Circulation.—Each of the general anesthetics brings about circulatory changes peculiar to and characteristic of that special agent. With all anesthetics the pulse rate is increased before consciousness is lost, due to psychical influences, and when ether is administered it is fuller and stronger. As narcosis develops it becomes more nearly normal in rhythm and force. Circulatory depression occurs most frequently under chloroform and may develop early in the induction period. When a weak, thready or irregular pulse is associated with pallor of the nose extending band-like past the corners of the mouth, circulatory failure is imminent and is best treated by withdrawing the anesthetic and stimulating efficient respiration so as to eliminate the anesthetic as rapidly as possible and assist the circulation of blood through the lungs and its return to the left auricle. If there has been a considerable loss of blood or if the head has been raised during chloroform anesthesia, anemia of the circulatory center may be the cause of the cardiac depression, and should be treated by the Trendelenburg posture, to refill the cerebral vessels. If the pupil is dilated and does not react to light, toxic paralysis of the medullary centers is present.

Blood Changes under Anesthesia.—Immunity, Coagulation, Leukocytosis, Specific Gravity.—As the blood is the carrier of the anesthetic in all forms of general anesthesia, it is important to know how it is affected by these agents. This knowledge is of special value in the selection of an anesthetic for operation on subjects who are debilitated from disease or who are already suffering from pathologic blood conditions.

Much experimental work has been done on immunity in its relation to surgical anesthesia, and until the valuable work of Mann was published, it was generally accepted that the inhalation of anesthetics depressed phagocytic activity, which lasted over a period of from two days to several weeks.

Graham,* working with the typhoid bacillus, studied the effects of ether on the phenomena of bacteriolysis and agglutination. The experiments were conducted *in vitro* by adding ether in varying amounts to both normal and immune typhoid serum, and also *in vivo* by observing the effects of ether anesthesia on these properties of the serums of practically normal human individuals, normal rats and rabbits that were immune to typhoid bacillus. In none of the experiments was there observed any appreciable effects of the drug on bacteriolysis. There was also no alteration in the phenomena of agglutination in the test tube or after anesthesia. Graham found that "ether added to both normal human and rat serum *in vitro* in varying amounts from 1 per cent. to 2.5 per cent. reduced the phagocytosis of steptococci. Likewise after ether anesthesia, a similar reduction of phagocytosis was observed with streptococcus, pneumococcus, staphylococcus aureus, B. coli and B. typhosus." It was observed that "rectal injection of olive oil was followed after three to six hours by a restoration of phagocytic powers likewise when lecithin was injected subcutaneously into etherized animals, the phagocytic power of the animal's blood was restored to its pre-anesthetic condition in a few hours."

Casto,† from his own studies and an extensive review of the literature, concludes that hemoglobin is always reduced by chloroform, ether and nitrous oxid, and that leukocytosis is increased under all anesthetic agents. He states that "the acid production of metabolism may be increased under anesthesia when deep cyanosis is permitted to occur or continue, but when a sufficient supply of oxygen is provided, this may be prevented."

Hamberger and Ewing‡ concluded from their researches that under nitrous oxid anesthesia, the hemoglobin is not permanently reduced, hemolysis is not increased; the changes in the hemoglobin and erythrocytes are transient and of no surgical significance. The changes in the coagulation time are not constant. Under ether anesthesia, the hemoglobin is slightly reduced; hemolysis is not increased; and a decrease in the coagulation time is most marked from 7 to 10 days after anesthesia. Under chloroform anesthesia, the hemoglobin is reduced, hemolysis increased and a decrease in coagulation time most marked from 7 to 10 days after anesthesia.

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* Graham, J. A. M. A., liv (1909), p. 1043.

† Casto, "Year-book of anesthesia and analgesia" (1915).

‡ Hamberger and Ewing, J. A. M. A., li (1908), p. 1586.

These findings are in conflict with the more recent studies of Mann whose investigations were conducted upon healthy animals without operative trauma, consequently the condition could not be influenced by any physical ailments or operative procedures. According to the results of Mann's studies, the generally accepted teaching that ether destroys immunity has abruptly become an open question. Mann* investigated the blood changes in healthy dogs not subjected to operative trauma. This author found: "That, as a rule, after a 10 hour etherization, there was no change either in the number of red cells or the hemoglobin content. Occasionally the white cells increase in number within the first hour of anesthesia, but frequently not until after four hours. The increase may be very slight, in some animals not above the coefficient of error, but usually by the end of the fourth hour of anesthesia, the number of white cells has doubled. The leukocytosis is not always progressive. Frequently a maximum number is reached which more prolonged etherization does not change. Sometimes there has been a decrease before the end of anesthesia. Usually, however, the number of white cells does not begin to decrease for a few hours after the animal has recovered from the anesthetic, and is still above normal 24 hours after etherization."

The leukocytosis just described is practically a constant and general phenomenon. It is not limited to the peripheral circulation, for the white counts are the same in the blood from ear veins, femoral veins and mesenteric veins. This fact, that the white cells are increased in the blood in widely separated parts of the body, also eliminated the possibility that stagnation to dependent parts or reaction to external irritation were factors. Such leukocytosis occurs in animals in which a moderate leukocytosis is present already. It resembles a leukocytosis of digestion. All of Mann's experiments, however, "were performed on dogs that had not had food from 12 to 24 hours. It differs from the leukocytosis produced by drugs, such as pilocarpin, in the fact that it is not a lymphocytosis, and atropin does not prevent its occurrence.

The spleen is not an important factor in its production, for it occurs also in animals that have been splenectomized. Its cause and site of action have not been definitely determined, but it would appear that it is a direct stimulation of the bone marrow.

Differential counts of the blood before and after ether show that there may be an actual increase in all of the forms of white cells, but that the polymorphonuclear cells are usually the only form noted showing also a relative decrease. The large lymphocytes usually decrease relatively, while the small lymphocytes always decrease.

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* Mann, Am. J. Surg., Anesthetic Sup., xxx (1916), p. 111.

The transitional cells usually show an increase. In one experiment, the eosinophils increased greatly. The size and character of all the cells remain normal.

In previous studies, the white cells have usually been subjected to artificial environment. They were separated from the blood, suspended in salt solution and, after the addition of the substance with which they were to be tested, such as carbon particles, were incubated for definite periods of time.

It was deemed of value to determine whether phagocytic activity was altered when the cells were subjected to the concentration of the ether such as occurs in the blood under surgical anesthesia. In order to make conditions as nearly normal as possible, the following method was employed: Under local anesthesia, one of the jugular veins was exposed, dissected entirely free from surrounding fascia and doubly ligated, a section about 10 cm. long partially distended with blood being left between ligatures. A suspension of Bacillus coli in salt solution was injected into this natural incubation tube, and after it was thoroughly mixed by rolling gently between the fingers, the skin was closed over the vessel. Under these conditions the blood does not coagulate, the phagocyte remains in its normal medium at approximately its normal temperature, and has access to the bacteria in approximately the natural way. After various intervals of time, an hour being found the most suitable, smears were made. These slides were used as controls. After definite intervals of etherization, the process was repeated on the other jugular vein with exactly the same technique. The cells in the latter vein had been subjected for several hours to a concentration of ether strong enough to maintain the animal under surgical anesthesia.

The blood smears were stained, and a count of the phagocytes containing bacteria and the phagocytes without bacteria was made. Usually 200 white cells were counted on a slide, and frequently counts were made on several slides from one vein. The average was taken as the final result. Only the polymorphonuclear cells were included in this count. The occasional large lymphocyte or eosinophil containing bacteria was ignored." It is obvious that there are chances for error in the method, but Mann does not believe the average error exceeds 10 per cent.

The results show that phagocytes which have been subjected for from four to six hours to a concentration of ether which is capable of maintaining a dog under surgical anesthesia do not exhibit any marked changes in activity. In most of these experiments the greater number of cells containing bacteria was found in the blood subjected to the ether, but the increase was not sufficient to be of positive significance. It can be definitely stated, however, that there was no decrease in the phagocytic power of the cells in the blood subjected to etherization."

Summary.—A study of the blood of dogs subjected to etherization demonstrated the following facts: The amount of circulatory blood is diminished about 10 per cent. after from six to nine hours of light etherization. There are variations in the cholesterin values, but the changes are not uniform. The specific gravity does not change under light etherization, and under deep anesthesia increases only as asphyxia becomes a factor. The number of red corpuscles, the amount of hemoglobin, and the fragility of the red cells do not change. There is always a leukocytosis in ether anesthesia. The degree of leukocytosis varies from a very slight increase in the number of cells to more than double the normal number. The increase is usually present after from three to four hours of etherization, and is due mainly to cells of the polymorphonuclear form. The leukocytosis is not dependent on the spleen and is not prevented by atropin. It is probably the result of a direct action on the bone marrow. Phagocytic action is certainly not depressed by an etherization period of from five to six hours. Observation seems to warrant the conclusion that chloroform prolongs the coagulation time, while ether hastens it.

General Considerations.—Operations that might be performed under local anesthesia in the adult frequently require general anesthesia in children. This is especially true when the operative measures require the quiet repose of unconsciousness. Local anesthesia becomes more important the older and more intelligent the child is. Children above the age of 12 or 15 may be treated as adults; for them the ordinary routine may be adopted. As children are very easily asphyxiated the open method of anesthetization is advisable, although this accident may occur with any method of anesthesia unless care is taken to watch the blood oxygenation either by noting the color of the ears, face and lips or the shed blood at the operation field. Children are much more easily and quickly narcotized than adults and are much more easily and quickly affected fatally by anesthetic agents; that is to say, the margin between a correct dose and an overdose is comparatively small.

The sighing and sobbing breathing which occasionally follows a period of crying before narcosis should not be mistaken for a light anesthesia as an overdose may be easily given under such conditions. When placed prone, feeble or rickety infants whose respiration is very commonly feeble, and those who have fluid in their chests, must be carefully watched as any mechanical interference with breathing may cause fatal accidents. Children are highly susceptible to surgical shock following a hemorrhage which would be of little moment in the case of an adult. Prolonged operations, especially if chloroform has beena dministered, frequently depress their vitality to an unusual degree.

Respiratory diseases are common in children, while cardiac and renal diseases which would make general anesthesia extra hazardous are not common in early life, they may occur, consequently children should receive a careful physical examination before being anesthetized.

As a general anesthetic for routine use, ether is to be recommended. In point of safety it is immeasurably superior to chloroform or nitrous-oxid-oxygen for the young. In infants and young children nitrous-oxid-oxygen is frequently an unsatisfactory and dangerous anesthetic agent, because of the liability of asphyxia. In selected cases nitrous-oxid-oxygen may be given to children over six years of age with a fair degree of safety providing an experienced anesthetist is the administrator. Children bear air limitations badly, therefore high percentages of oxygen must be given with the nitrous-oxid. A few inhalations of nitrous-oxid-oxygen or ethyl chlorid may be given preliminary to the ether anesthesia as it makes the induction period shorter and pleasanter. However, if ether is given by the open method, allowing an abundance of air, and the administration is slowly conducted, it is taken much better than is generally supposed. Chloroform has been a popular anesthetic for children because of the readiness with which anesthesia can be produced and the erroneous impression that children are immune to its poisonous effects.

Children with hypertrophied tonsils and adenoid growths have more or less difficulty in breathing, depending on the degree of obstruction, and because of the very high mortality under anesthesia, the theory was advanced that a "lymphatic diathesis" existed in these patients which rendered them more prone to circulatory depressions. In reviewing the literature, one is impressed by the dominance of deaths occurring under chloroform anesthesia and at once the question arises: Would these deaths have occurred if ether had been administered? In a continuous series of 5042 operations for hypertrophied tonsils and adenoid growths performed in the Presbyterian Hospital, Chicago, there were no fatalities. One is constrained to wonder if the good fortune has not been due to the anesthetic administered, as it is only just to assume that there must have been a few cases of the so-called "status lymphaticus" in such a large number of patients.

The causative factors in the fatal cases have been given as shock, due to surgical interference with the sensitive region of the nasopharynx, incomplete anesthesia, etc.

Hewitt has pertinently said: "Before admitting a pathological entity could cause death, we should satisfy ourselves that death could be explained on no other ground. Distinction should be made between death due to the lymphatism and death due to other causes. Certain anesthetics predispose to sudden death when particular pathological conditions are present." The truth of this cannot be questioned, but the judgment of the anesthetizer must be questioned when that "certain anesthetic" is administered under such conditions.

General anesthesia is more often required in children for purposes of examination than with adults, this applying particularly to severe injuries of bones and joints. The examination, reduction, operative measures and dressings can be done under the same anesthesia. Such minor operations as tenotomy for club foot, circumcision, the first dressing after a severe burn, incision of the membranum tympani, application of the Paquelin cautery, electrolysis for nevus, should be performed under a light general anesthesia. Tracheotomy should be done under general anesthesia unless the child is unconscious from asphyxia or sufficiently old to permit a local anesthesia to be used. Intubation requires no anesthesia. Pyloroplasty, which can be performed through a small incision, may be satisfactorily done under local anesthesia in infants a few weeks old, while gastro-enterostomies call for a general anesthesia. In the latter operation crying and straining forces the intestine through the abdominal wound and materially complicates the operation.

Convulsions may occur in both the symptomatic and idiopathic types of epilepsy during the induction and maintenance of narcosis, regardless of the anesthetic used or the method of its administration. The epileptic cry is occasionally heard during the induction period, but seldom occurs after narcosis is established. In the severe forms of epilepsy, some observers are of the opinion that in practically every instance either a petit or grand mal occurs during the induction of anesthesia. A seizure prolongs the induction period and usually causes cyanosis of a marked degree, which disappears at the close of the attack. The seizures during narcosis vary in number and intensity, and are frequently preceded by an increase in the salivary secretion. During an attack, nystagmus may develop and the pupils become unevenly contracted. There is frequently grinding of the teeth or a firm fixation of the jaw, with more or less embarrassment to respiration, which is of a noisy type. Clonic or tonic spasm of the muscles of the extremities, neck and jaw may be present, while the abdominal muscles are sufficiently relaxed for operative procedure. As a rule, the pulse is not affected by an attack. The pre-anesthetic preparation of epileptic patients is important, as they are nearly always constipated, and in more or less of an acidosed condition.

The glandular system is differently affected, not only by different anesthetics but by different stages of the same anesthesia. For example: There is greater activity of the mucous, salivary and sweat glands under ether than under chloroform, and at the beginning of anesthesia than when narcosis is established. If "shock" develops, the mucous secretion ceases while the sweat glands are active, the dry skin or warm perspiration being replaced by a "cold sweat" which is especially noticeable about the face.

The extent to which hemorrhage will modify the phenomena of anesthesia will depend upon the general physical condition of the patient and the amount of blood lost. The pulse will be more seriously affected by the sudden loss of blood than if the same amount were lost over a longer period of time. Anemic patients require very small quantities of the anesthetic to induce and maintain narcosis. These subjects are very intolerant of air limitations, the asphyxial state developing in a remarkably short time, especially if nitrous oxid is given with insufficient oxygen. Three or four inspirations of pure nitrous oxid are sometimes sufficient to produce clonic spasms or epileptiform movements, which condition always indicates an asphyxial state. Cachectic and feeble children require remarkably small doses of any anesthetic. Shock is precipitated by hemorrhage and is indicated by pallor of the face and surface of the body, cold sweat, especially of the forehead, and a rapid small pulse which becomes irregular in force and rhythm. When this condition supervenes, the anesthetic must be suspended, as pain sensation is no longer present. Infants, anemic and cachectic subjects are naturally more seriously affected by the loss of blood than the robust individual, and consequently must be closely watched, and if depression develops, little if any anesthetic administered. The greater the quantity of blood lost, the smaller the amount of anesthetic will be required.

It has been observed that there is considerable difference in the rate of respiration in individuals of normal health. Generally those who breathe slowly are slow of action and speech, and it has been claimed that in such patients there is a difference in the vitality of the respiratory center, and there exists a greater tendency to respiratory depression.

The drowsy or semi-conscious patient will require very small quantities of the anesthetic. When coma is present, no anesthetic is indicated. Patients suffering from depressed fractures, intracranial hemorrhage and cerebral abscess are frequently in a more or less comatose or lethargic state, and will require little anesthetic. Subjects of cerebral and cerebellar tumors may display symptoms of respiratory failure from increased intracranial tension, and should such a patient be anesthetized even lightly, breathing may be completely suspended.

Inspection and Examination of the Patient.—Positive and negative information may be gained by observing the general appearance and bearing of the patient. Notice whether he becomes breathless on exertion, the position which he voluntarily assumes on the table and whether he wishes his head high: All this affords information. Those who are suffering from diseases of the air passages or extreme abdominal distention insist on being propped up, while those with unilateral pulmonary affections will probably lie on the affected side. The presence of pain may induce the opposite posture. The pallor of true anemia is readily recognized. The manner of respiration, and dyspnea, particularly if associated with cyanosis and marked pallor and duskiness, should be investigated, as also feebleness, irregularity, intermittency or slowness of the pulse. These observations are necessary in order that the most appropriate anesthetic may be selected. The mouth should be examined for loose teeth in children at certain ages, lest they become dislodged during the anesthesia by the insertion of gags or by wiping out the mouth.

Anesthetizing Children.—Kindness, gentleness, a smile, a cheerful word and good temper are important elements in the success of an administration in children. If for the moment the anesthetist will adopt the patient's point of view, he will feel a greaterch arity for his fright, anxiety or distress. Whether it is better to tell a child of the contemplated operation will depend much upon the nervous stability and intelligence of the child; however, the alarm which they sometimes feel is usually due to the parents or sympathetic friends who by their conversation or conduct have betrayed their anxiety. Whether the parents or friends should be allowed in the anesthetizing room will depend very largely upon their self-control. An agitated, crying relative, talking constantly and telling the child not to be afraid or that nothing is going to be done, will enhance the difficulties of the anesthetist twofold, as under such conditions it is impossible to control and direct the child's mind into pleasant channels. Such an individual will make an otherwise calm child frightened and fearful that something very dreadful is going to happen to him. On the other hand, a parent or relative who has his emotions well under control, and the child feels less disturbed when they are with him, may with advantage be allowed in the room till unconsciousness supervenes. Make the acquaintance of the patient, if this has not already been done, before starting the administration of the anesthetic. A few moments of playfulness with children of tender years will soon reassure them; while with older children an effort should be made to find out what they are interested in. If attending school, questions about their school work or the games they are fond of and how they are played. All children like to hear stories and at times enjoy telling them. After securing their confidence, tell them what you are going to do and why you are going to do it. Make them feel that everything that is done, is done for their good and that it is to help them to get well. If a child is old enough to reason, it is remarkable how their coöperation can be secured by a little tactfulness. A rule which should be made absolute is, that there shall be no misrepresentation. Children are quick to detect deceit and are slow to forget it, and when this is practiced, the child is made more intractable for future anesthesias. The same management will not control the mental attitude of all children. After an acquaintance is established, tell him that you are going to give him some medicine that will make him go to sleep, and that when he awakens he will be back in his bed. This can usually be told in the form of a joke and will impress the child as being funny. The older and more alert children become interested at once in the apparatus used, and want to see it and ask questions about it. Before placing the protective moist cotton pad over the eyes, show it to the child and explain what it is for. If they are freightened or object to having their eyes covered, they can usually be persuaded to place it over their eyes themselves. After starting the anesthetic, never speak of it or in any way call the child's attention to it, as, for example, asking if he is asleep or if he likes the odor. On the contrary, if he speaks of it and you are unable to hold his attention by a story you are telling, ask him to tell you one and ask him questions about the things in which you had previously found he was interested.* When a child can be thus controlled, the usual method of induction is employed.

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* The author once met in the hospital corridor a child whom she had anesthetized, and after an exchange of greetings, she was informed that the only regret he had over his operation was that he went to sleep before he "heard the finish of the story."

When gas and oxygen are used alone or as a preliminary to ether, narcosis develops so quickly that there is no time for entertainment, but when ether alone is given and the child can be managed through mental control, the method of administration differs in no respect from that used for adults, that is, by gradual induction. Children under five or six years of age and occasionally older patients cannot be thus managed, in which case they will have to be held or restrained during induction. Crying for obvious reasons hastens narcosis. If chloroform is being administered, great care must be exercised lest a crying child inhale deeply, for a few such inhalations, especially if the vapor is at all concentrated, will be sufficient to paralyze the heart.

Preparation of the Patient for General Anesthesia.—To secure an ideal anesthetization, it is essential that attention be paid to details before and during the administration of general anesthetics. This is important in the so-called minor as well as major operations. It is a generally accepted fact that the best time for the administration of an anesthetic is in the morning. Patients are not only fresher and brighter after the night's rest, but the stomach is then empty and in a state of quiescence. On the day preceding the operation, there should be as little deviation as possible from the child's usual routine. Children in good health may be allowed their usual meals; however, it has been observed that if the carbohydrates (oatmeal, sugar, the fruit juices, etc.) are given with a restriction of hydrocarbons, that there is less likely to be vomiting or the development of acidosis. Glucose is valuable as a food and helps to combat acid intoxication. It may be given three or more times a day with water and lemon juice before operation, and by rectum or intravenously (2.4 per cent.) following operations. In cases of toxemia, especially in victims of a subacute or chronic affection, more sugar than can be given by mouth should be administered. In this type of cases, the rectal administration of 4.5 per cent. anhydrous dextrose works very well. In this connection, the examination of the urine for aceton and diacetic acid should not be neglected, and if present, an alkaline treatment should be instituted. The quantity of alkali which is required to make the urine alkaline is an indication of the amount of aceton present in the body. Bicarbonate of soda is the alkali which is best borne and can be taken in the largest amounts. It can be given in from 5 to 10 gm. doses, in plenty of water every two or three hours. The fruit juices are oxidized into carbonates and consequently represent an alkali administration. As a general rule, no solid food should be taken for at least six hours before the administration of a general anesthetic. The author has frequently encountered difficulties of a respiratory character due to the presence of undigested food in the stomach. A smooth, even anesthesia is almost impossible when the stomach is distended, as respiration is more or less embarrassed, and unless the patient is profoundly anesthetized, there will be retching or vomiting, with the added danger of aspirating pieces of undigested food into the bronchi, with a resulting pneumonia, lung abscess or immediate death through strangulation. Debilitated children may be allowed small quantities of easily digested food, as gruels of barley or rice, up to within three or four hours of the operation. Infants should be nursed up to within two or three hours of the operation. In emergency operations, the stomach may be emptied through the stomach tube in the children who are taking solid food. The bowels should be moved by a mild laxative the night preceding, and an enema a couple of hours before the time set for the operation. Age permitting, the child should be encouraged to empty the bladder before narcosis is induced. Children should never be given any of the opium derivatives, because of the added danger to respiratory embarrassment when these are given with anesthetics. A physical examination should be made of the chest for pathologic conditions of the lungs and heart, and the urine for aceton and diacetic acid, blood, albumin and casts.

Posture, Change of Posture, the Transference of Unconscious Patients.—The posture of patients during general surgical anesthesia is a matter of greater importance than is generally imagined. The dorsal posture, with the hands on the table at the sides and the head in the body line neither flexed nor distended and the face turned to the side, should be adopted whenever practical. As a rule, children do not require a pillow.

Flexion of the head throws the base of the tongue against the pharynx and obstructs breathing. Extension carries the epiglottis away from the glottis, thus exposing the larynx to the entry of foreign substances. Turning the head to the side prevents the tongue from falling back in the pharynx and obstructing respiration and allows the mucus to pass out of the mouth instead of running back in the trachea and causing coughing. For tonsil and adenoid operations, the lateral posture is desirable, as it is least likely to be associated with any respiratory embarrassment from the presence of blood. Anesthesia may be induced in the dorsal position and the patient changed to the lateral after narcosis is established. Children over seven or eight years of age usually require a pillow to keep the head in line with the body when placed in the lateral posture. When the prone posture is necessary, as it is for such operations as laminectomy and cerebellar tumors, an endeavor should be made to avoid respiratory embarrassment by placing sand-bags under each shoulder, thus facilitating lung expansion. Breathing must be watched if a change in posture becomes necessary. Mucus and saliva may trickle or flow from one part of the upper air tract to another, causing coughing or vomiting, or the tongue may fall back in the pharynx and obstruct respiration. Cyanosis with other asphyxial phenomena are more apt to follow a change in posture during light than deep anesthesia, while syncope is more likely to develop during deep narcosis if the patient be raised from the horizontal into the sitting posture. This danger is especially great if chloroform has been given. In bandaging the chest or abdomen, the patient, if an infant, can be lifted from the operating table and kept horizontal, while older children can be brought over the end of the table and so held, with the head on a level with the body.

The Transference of Unconscious Patients.—For reasons already given, it is most desirable that patients should be anesthetized upon the table to be used during the operation, and not in their beds or upon carts. It is especially hazardous to transfer those suffering with respiratory or circulatory affections.

Posture Paralysis.—Nerve roots or nerves themselves may be so compressed or stretched that paralysis in varying degrees may result. The most common posture paralysis is the one which occurs after long operations, during which time the arm has been abducted and drawn upward, the deltoid, biceps, brachialis anticus and supinator longus being affected. If the hand is allowed to hang over the side of the table, the musculospiral nerve may become compressed between the humerus and the table edge, with a resulting paralysis. The application of an Esmarch bandage may induce a temporary motor or sensory paralysis. Complete recovery from these various posture paralyses generally takes place within a few weeks or months. However, it may be delayed as long as a year and a half. Recovery usually takes place from the periphery toward the center.

After-care of Patients.—After the completion of the operation, all wet or soiled clothing should be removed and a warm dry gown put on, and the patient well covered with woolen blankets for the journey back to his room. It is a well-known fact that pneumonia frequently develops in a robust person after an exposure to wet or cold. We all harbor the organisms of pneumonia and all that is necessary for the development of the affection is a lowered vitality. The question naturally arises whether many of the post-operative pneumonias might not be prevented if greater care were exercised in preventing loss of body heat during and following operations. The bed to which the patient is to be transferred should be warmed by means of hot bottles, which should be removed before the patient is placed in it. A large number of cases have occurred in which hot-water bottles have produced burns during the unconsciousness of the recovery period.

Nausea and Vomiting.—Provided the patient has been properly prepared, which is of paramount importance, the administration skillfully conducted and pure anesthetics used, there will be no trouble from nausea and vomiting during the induction of narcosis. Vomiting during maintenance occurs only when a light anesthesia is present, the medullary center being irritated but not narcotized. Transient retching with the expulsion of a yellowish fluid may develop after the anesthesia is discontinued, while the patient is still unconscious. This is an advantage, as it clears the upper air passages of mucus and the stomach of fluid and any anesthetic which may have been excreted into it. Vomiting following throat and mouth operations is desirable and to be expected on account of the blood which may have entered the stomach during the operative procedures or have been swallowed during returning consciousness. Vomiting following anesthesia is much less common in children than in adults, and if persistent, acidosis should be considered, and the urine be examined for acetone and diacetic acid. This is especially important if chloroform has been administered.

The persistent vomiting of acidosis is relieved only by measures employed to combat the acid poisoning: Bicarbonate of soda per rectum, or intravenously in desperate cases. Fecal vomiting ceases only when the obstruction which caused it is removed. The patient who is vomiting should have his head kept turned to the side and the opposite shoulder raised. There is some danger of suffocation or aspiration of vomited matter into the trachea if an unconscious child is placed in the prone position following tonsil and adenoid operations, unless well attended.

Respiratory and Circulatory Embarrassment and Arrest.—In order to understand the various ways in which respiration may be arrested it is necessary to understand the respiratory phenomena of general surgical anesthesia and the factors which may influence the character of respiration, the various conditions, local and general, which may predispose to respiratory arrest and the type of patients which are most likely to exhibit respiratory embarrassment. There are two fundamentally distinct forms of suspended breathing, mechanical or obstructive and central or paralytic. Mechanical or obstructive may be trivial and easily corrected by a change in the position of the head, pushing the jaw forward, by removing some adventitious substance in the mouth, or by loosing tight clothing or bandages. Other mechanical obstructions which may tax the utmost resources of the anesthetist are swellings or growths within the larynx, within or without the trachea causing pressure or deflection of that structure, fluid in the chest, abscess of the lung which may be discharging into a bronchus. Portions of tonsils or adenoid growths, loose teeth, pieces of bone or fragments of tissue from operative procedures in jaw cases may become dislodged during operations within the mouth or nose and obstruct breathing. If a tooth, or a fragment of one, escapes into the pharynx and is not swallowed it may remain for a considerable time in the epiglottic region and later be forced out by coughing or it may be aspirated into the larynx or bronchus. Should the latter occur, coughing of a spasmatic character may be excited and the substance at once dislodged. If narcosis is profound coughing may be slight or altogether absent. If the foreign body lodges in the pharynx urgent symptoms such as stridor, cyanosis and complete cessation of respiration may occur. Conditions below the diaphragm may prevent lung expansion. Most of the inspiratory work is done by the diaphragm and it is therefore important that this muscle should not be impeded, especially in those subjects in whom the thorax is unable to work. In hydrothorax, plural or pulmonary disease or in excessive abdominal distention blood oxygenation may be sufficient during consciousness but ceases to be so when the accessory muscles of respiration are paralyzed during anesthesia.

Paralytic cessation of breathing is the result of failure of nervous energy, due to an overdose of the anesthetic alone or in combination with some opium derivative acting upon the respiratory center or from cerebral anemia due to low blood pressure. The anemia may be caused by the sudden sitting posture or, as more frequently happens, by hemorrhage at the field of operation with accompanying shock. In mechanical interference with the free entry and exit of air the narcosis may be light or moderately deep while those derangements which are dependent upon central causes occur during deep anesthesia. The latter are very serious and must be treated by supplying air or oxygen by artificial means. An overdose of nitrous oxide induces muscular spasm about the air passages so that such respiratory failure is of a different type to that which occurs during ether or chloroform narcosis. In the latter case the failure is more or less gradual, the breathing growing more and more shallow till it ceases altogether or cessation may be preceded by "jerky" respiration. Should the pupil be widely dilated and inactive to light, grave danger is present and the administration should cease at once. Make sure of a clear air-way and assist respiration by pressure on both sides of the chest wall during expiration and the actual cessation of respiration may thus be averted. Should respiration cease, which will be known by the absence of thoracic and abdominal movements and the duskiness of the face, systematic artificial respiration must at once be resorted to. Patients under the influence of sedatives, as opium or its derivatives, are most likely to have this form of respiratory arrest and the delay in the reëstablishment is as much or more dependent upon the action of the sedative as upon the action of the anesthetic. Recovery may take place after all signs of respiration and circulation have disappeared, therefore artificial respiration should be kept up as long as there is the slightest chance of resuscitation.

The author cannot too strongly dissent from the teaching that no attention be paid to the pulse during narcosis, but to rigidly watch the breathing. There are many instances in which the pulse indications are of the greatest value and the anesthetist who ignores them or is unable to properly interpret them is a menace to the surgeon as well as the patient. Not infrequently the anesthetist may impart valuable information to the surgeon as to the true condition of the patient by his reading of the pulse as well as the respiratory phenomena. Primary pulse disappearance from a toxic dose of the anesthetic is an exceedingly grave symptom and immediate and vigorous measures at resuscitation are urgent. Extend the head over the end of the table so that the respiratory center may be better supplied with blood, see that the air-way is clear and proceed to perform artificial respiration, which is the best cardiac stimulant. In case these measures fail to resuscitate the patient, direct massage of the heart may be tried. This procedure has been successfully practiced in a few recorded instances but further observation, however, is necessary before anything definite concerning its advantage can be positively stated.

Leading authorities are of the opinion that drugs are of little or no value in the treatment of respiratory and circulatory failure due to anesthetic agents. The withdrawal of the anesthetic and the establishment of a free air-way and artificial respiration are of far greater value than any drug stimulation when an overdose has been administered. Strychnin, digitalis, atropin, adrenalin, ergotin camphorated oil all have their advocates but it is questionable whether they are of any real value. Shock is best treated by hypodermoclysis with normal salt solution which in desperate cases may be done during operative procedures. Better still is the intravenous use of colloidal (gelatin) solutions* or by direct transfusion.

Different Methods of Producing Anesthesia.—A considerable amount of literary, scientific and inventive energy has been expended in developing the practical side of anesthesia. The most important, perhaps, is the increasing recognition of the fact that with all anesthetics there is a tendency for obstructed breathing to take place and for anesthesia thus to be complicated by varying degrees of asphyxia; further, a proper appreciation of the influence of posture during anesthetization has also tended to improve results with all anesthetics.

There are so many recognized methods of administration that, providing the anesthetist be thoroughly competent, anesthesia may be produced with little fear of an unfavorable outcome. There is perhaps no question in connection with the actual administration of anesthetics which is more discussed at present, than which is the best method of administration. The whole subject of anesthesia is in an unsettled state, principally by reason of the recent introduction into practice of several ingenious instruments by which the regulating of the percentage composition of the anesthetic agent may be secured, together with the different methods of introducing the agent into the system by other channels than the respiratory system. Whether this wave of ingenuity will pass as others of like nature have passed and the simple open method be universally employed, it is impossible to say. Not only are different views held in different sections of the country, but individual members of the same section hold different opinions according to the schools in which they have been educated or the appliances which they have studied or originated. Interns and medical students certainly should be taught methods of administration which they will be able to apply in practice. To insist upon their administering anesthetics by means of some more or less complicated apparatus which may and frequently is unattainable in practice, is unfair both to the student and the general public with whom they will subsequently deal.

The different methods for the induction and maintenance of ether anesthesia are the inhalation, venous or arterial, and rectal. In inhalation anesthesia, as the term indicates, the anesthetic is breathed and enters the system through the lungs. It may be delivered to the patient by the open, valvular, closed or re-breathing, intrapharyngeal and intra-tracheal methods. In the open method, a copious quantity of

* Hogan, J. A. M. A., lxiv (1915), p. 721.

atmospheric air gains access to the lungs throughout the anesthesia and all expirations escape into the surrounding air. The term "semi-open" is applied to the method when a limited amount of air is admitted.

Open Ether.—The Open Method of etherization was originated and developed by Dr. Lawrence H. Prince in 1893. At that time he gave a description of the method and reported two series of administrations each containing 500 patients.

The superiority of the method is evidenced by its steady growth in popularity.

According to the statistics of the Committee on Anesthesia of the American Medical Association more than half of the ether anesthesias administered from 1905 to 1912 were by the open method. This method of administration does not preclude sequence or combined anesthesia if desired, nor does it mean that the anesthetic cannot be selected to suit individual requirements. Furthermore, the simplicity of the method should not argue against its efficiency.

A 4 to 8 ounce can of ether, the size depending on the estimated time required for the operation, is fitted with a cork, into the opposite sides of which two V-shaped grooves of unequal size are cut. In the larger of the two grooves is placed a wick of cotton which reaches nearly to the bottom of the can and extends about an inch beyond the cork. If the cork and wick are properly arranged, a full, steady drop will be secured. The rate of drop can be controlled by the angle at which the can is tipped. A cone covered by two layers of fairly fine, closely woven stockinet, or its equivalent in gauze, is used.

Technic of the Open Method.—The manner in which ether is administered during the induction of narcosis spells comfort or discomfort for the patient and makes for his future attitude toward anesthesia. Ether may be given as a sequence to nitrous oxid and oxygen which doubtless is the most agreeable method for the patient. However, many hospitals are not equipped with an apparatus for the administration of nitrous oxid and oxygen, consequently a method which gives the greatest amount of comfort to the patient and at the same time is safe is most desirable. Ethyl chlorid and ethyl bromid may be given in place of the nitrous oxid and oxygen. They possess the advantage over nitrous oxid and oxygen in that they are more easily carried about and require no special apparatus for their administration, but the mortality attendant upon their use is so high that few anesthetists care to assume the extra risk of administering them.

Preparation of the field of operation during the induction of anesthesia serves a double purpose. It shortens the length of narcosis and helps to divert the mind of the patient from the anesthetic. The confidence and coöperation of young children as well as adults can be readily secured if a moment is taken to explain what you are going to do and why you are doing it.

Before beginning the anesthetic the patient is told to breathe naturally, not to force his respiration, and while the mask is held away from the face the ether is slowly dropped on various points of the cover. As the patient becomes accustomed to the odor the mask is gradually lowered till it rests on the face. The rate of dropping is now increased until the entire cone cover is moist. In a few minutes a piece of gauze is placed around the cone or the cone may rest on a gauze ring pad which encircles the nose and mouth, to shut out the air which passes under it, thus all the air which the patient receives is more or less impregnated with ether vapor. When the cone cover is too thick, as, for example, when two layers of stockinet and 10 or 20 layers of gauze are used, the method ceases to be open and may be termed the semi-closed method. With the latter technique more ether is required to moisten the cover, and the patient's exhalations to a considerable degree are retained within the cone and are re-inhaled. The oxygen supply is thereby greatly diminished, the effect of which is shown by greater or less cyanosis. Two layers of fine, closely woven stockinet or its equivalent in gauze is all that should cover the mask. Stockinet makes a better evaporating surface than gauze. If the cover is too thin it is difficult or impossible to induce and maintain anesthesia. The ether should be dropped continually on the cone. If the dropping is suspended till signs of returning consciousness appear an uneven narcosis results. Intermittent administration has the further disadvantage or danger of administering a too concentrated vapor in one's haste to get the patient under again. It should be remembered that a concentrated vapor will do more injury to lung epithelium in a few minutes than a dilute vapor will do during a long anesthesia. It has been shown that a 6 or 7 per cent. vapor is the greatest concentration which can be inhaled without irritation to the air passages. The depth of narcosis is controlled by the amount of ether dropped on the cone and can be varied to suit the operative requirements. To have the cone more than saturated is a waste of ether, as it runs off the cover. When the proper technique of the open method of etherization is carried out, narcosis develops like a natural sleep and it is a rare exception not to have a smooth anesthesia with relaxed muscles and perfect oxygenation throughout the most difficult operation. Contrary to the teachings of some anesthetists, we have no hesitancy in saying that, barring operations which call for insufflation (intra-pharyngeal, intra-tracheal) anesthesia, the open method is suitable for any patient or any operation in which ether is the anesthetic of choice. It has been employed in our clinic with equally good results at all ages ranging from 36 hours (spina bifida) to 96 years (carcinoma of the face), and in all conditions of health from the marasmic infant to the athlete, from the frail patient suffering with severe heart lesions to the obese alcoholic. Observation has clearly demonstrated that trouble during induction and maintenance is invariably due to faulty technique and not to the open method of etherization.

It is a mistake to think that this method is foolproof. An overdose of ether can be given easily, although the danger is not so great as when less air is allowed as in the re-breathing or closed methods.

Advantages of the Open Method of Etherization.—The superiority of the open method of etherization does not rest upon faith but upon demonstrated facts. One of the greatest, if not the greatest advantage which this method possesses is the large amount of oxygen which the patient constantly receives. This fact is readily determined by observing the ears, face and color of the blood. There is not an intermitting pink and duskiness as when the re-breathing method is used, but the blood oxygenation is constant and normal throughout the narcosis. It therefore naturally follows that the toxic effects are lessened and this has been shown to be true. Gatch's* studies lead him to the conclusion that: "The severity of the pulmonary lesions found after experimental etherization by the closed method can be satisfactorily accounted for by the great concentration of the ether vapor and the greater liability to aspirate mouth contents when these are used." Dresser† found that: "The ether vapor within the closed mask sometimes reached a concentration as high as 34 per cent. while 6 or 7 per cent. is the strongest concentration which can be inhaled without irritation to the air passages." He regards any concentration of vapor which cannot be inhaled by a conscious patient without coughing as harmful to the lung epithelium. Poppert likewise concluded from his experiments that the greater the ether concentration the more irritating to the lungs. Offergeld‡ studied the pathologic changes in the lungs which occurred after an etherization lasting from 70 to 80 minutes. His results were obtained in guinea pigs, rabbits and cats after using the closed method, semi-closed method and by the open method. The animals which did not die were killed at various periods after the narcosis. With the closed anesthesia some of the animals died in a few days from bronchopneumonia. Some were killed in two or three days and their lungs showed patches of bronchopneumonia, fatty degeneration and desquamation of broncho-epithelium and hemorrhage into the alveoli. None of the animals that were given ether by the semi-closed method died. If killed at the end of the first day, patches of consolidation with some blood and desquamation of epithelium were present in the bronchi. With the open method there were no deaths. Two days after the anesthesia, necropsy showed a perfectly normal condition of the lungs. When the closed method was used it required four days for the mildest cases to repair. The difference in anesthesia as maintained by the open and closed methods is quite apparent. When an asphyxial factor is introduced the accessory muscles of respiration assist in the effort to obtain a sufficient supply of oxygen. The result is labored breathing with more or less heaving abdominal movements. The presence of anoxemia is evident by the congestion of the venous system, as shown by the bluish color of the ears, lips, cheeks and blood. The respiratory tract is especially affected by the general venous engorgement which increases the size of the tongue and surrounding structures, and thus a mechanical obstruction is produced which is further aggravated by the increased flow of mucus. When an abundance of air or oxygen is allowed there is no congestion of the capillary vessels and consequently there is little oozing of venous blood from the wound. The pulse is of good volume and blood pressure is well maintained.

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* Gatch, J. A. M. A., lvii (1911), p. 1593.

† Dresser, Bull. Johns Hopkins Hosp., vi (1895), p. 7.

‡ Offergeld, Arch. f. klin. Chir., lxxxiii (1907), p. 505.

Fall in Temperature.—In a series of patients anesthetized by the open method we found the temperature (rectal), following operations lasting 35 minutes or more, averages a fall in the male patients of 0.67°F. and in the females 0.27°F. The patients upon whom these observations were made were well covered during the operations, as is our custom, the parts to be operated upon alone being exposed. Davis and McCarty,* in a recent publication, call attention to the fall in temperature during natural sleep. The observations were made upon children who were without fever and without ailments which might cause variations in temperature. The rectal temperature was taken just after the child had fallen asleep and again after an interval of two hours without waking the child. The fall during two hours sleep was 0.9°F. in the males and 0.41° in the females. Why the fall is so much greater in the males than in the females in both series we are unable to explain. It will be observed that the fall during natural sleep is twice as great as that during narcosis and, as these authors suggest, it is possible that the decrease in body temperature during etherization is analogous to that occurring in natural sleep.

The average temperature beneath the mask when ether is administered by the open drop method is about 32°C., that is, relatively near body temperature. We may therefore eliminate the necessity of any apparatus to warm ether given by the open drop method since the enclosed space in front of the mouth, provided by the cone, forms a natural warming chamber from which the air-ether mixture is delivered into the mouth at a temperature approximating that of the body. McCarty and Davis have shown that the further increase in heat in such cases is gained by the time the anesthetic has entered the lungs.

Conclusions.—(1) When ether alone is administered the induction of narcosis by the open method of etherization is comparatively comfortable.

2. With the open method of etherization, the blood is well oxygenated throughout the narcosis and the patient leaves the operating table with normal respiration and normal color.

3. Barring operations which call for insufflation anesthesia the open method is suitable for any patient or any operation in which ether is the anesthetic of choice.

4. Experimental evidence shows that with the open method of etherization there is less injury to the lung epithelium than when the closed or semi-closed methods are employed.

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* McCarthy and Davis, Am. J. Surg., Anesthetic Sup., 1 (1917), p. 46; Annals Surg. lxiii (1916), p. 305.

5. Trouble during induction or maintenance of anesthesia is invariably due to faulty technique and not to the open method of etherization.

6. The conservation of body heat during narcosis is of greater importance than warming the ether vapor.

Closed or Re-breathing Method.—The apparatus used in the closed or re-breathing method, as a rule, contains no valves, but is arranged with stop cocks, which are under the control of the administrator. Attached to the face-piece, which can be accurately coapted, is a bag, into and out of which the patient breathes, the air supply being intentionally restricted and the expiratory products retained for re-breathing. There is a progressive change in the composition of the imprisoned air in the bag corresponding to the duration of the to-and-fro breathing. The admission of fresh air or oxygen must be regulated by the susceptibility of the patient being anesthetized. Rapid and labored respiration, especially a strained form of expiration, cyanosis, and stertor are indications for more oxygen. It should not be forgotten that the anoxemic factor is almost as powerful as the ether factor in this method of anesthesia and therein lies the chief objection to the method. The patient should be slowly anesthetized by ether and a large amount of atmospheric air, and not by ether and his exhaled CO_2.

Valvular Method of Anesthesia.—In the valvular method of anesthesia, inspiratory and expiratory valves are present in the inhaling apparatus. When ether or chloroform is administered it is vaporized either by passing atmospheric air or oxygen over or through it. In this method, each inspiration contains a quantity of the vapor and each expiration escapes into the atmosphere. As a rule, the percentage of the anesthetic vapor may be estimated. This is especially true when a gas, such as nitrous oxid, is being administered.

Dosimetric Method of Anesthesia.—Generally speaking, it may be said that blood will continue to absorb anesthetic gases and vapors till an equilibrium is established between alveolar and blood tensions. It has been demonstrated that so-called "anesthetic tension" is practically the same in all classes of individuals.

There are various ingenious instruments by means of which definite percentage mixtures of ether or chloroform vapors and air or oxygen can be given.

Karl Connell* has devised an apparatus, the "anesthetometer," which undoubtedly comes the nearest of any apparatus now in use to being ideal in estimating the amount of air passing and the percentage of ether vaporized.

A safe percentage early in anesthesia may be a fatal percentage in the later stages. The rate and depth of respiration are important factors in the absorption of an anesthetic. A safe concentration to administer during normal respiration may become dangerous if the respiration increases in rapidity unless at the same time it decreases in depth, and this is especially true if cholorform is being administered.

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* Connell, Karl, J. A. M. A., lx (1913), p. 892.

For this reason, it is quite impossible to state as to what is or is not a safe concentration. It is evident, therefore, that the question of percentage vapor, like the question of oxygen percentage, resolves itself after all into the patient being the index rather than an apparatus which delivers the vapor, regardless of the perfection of the mechanical control of the anesthetic.

Anesthetic Sequence.—When certain anesthetics are administered in succession, the method is known as anesthetic sequence. Many of the disadvantages of employing a single agent may be eliminated by the successive administration of appropriate agents. This is well exemplified in the administration of nitrous oxid and oxygen before ether. Care must be taken, however, that appropriate sequences are chosen or unsatisfactory results may insue.

As a general rule, two agents are used, one being the initial and the other the terminal agent. Nitrous oxid and oxygen are particularly appropriate for inducing anesthesia, as it is not unpleasant to inhale and it destroys consciousness quickly. While ether is by far the best general anesthetic for ordinary surgical work, unless expertly administered during the induction period it is distinctly disagreeable to the majority of people. Consequently, the nitrous-oxid-oxygen-ether sequence is most desirable from the patient's point of view. Ethyl-chlorid-ether sequence has not proven as satisfactory as the nitrous-oxid-oxygen sequence. Ethyl chlorid is not so pleasant to inhale as nitrous oxid and is far more dangerous. The ether-chloroform sequence is safer than the chloroform-ether sequence because the stimulating action of the ether counteracts the depressing effects of chloroform. Chloroform has been extensively used as a preliminary to ether anesthesia, and it would seem particularly appropriate, as such a small quantity is required and few object to the odor, and no especial apparatus is required for its administration, but it must not be forgotten that most of the chloroform fatalities have occurred before surgical anesthesia was established, in fact, after the first few initial inhalations. The employment of this method subjects the patient to a far greater risk than the employment of ether alone, or the nitrous-oxid-oxygen-ether sequence.

Intratracheal Anesthesia.—In intratracheal insufflation, the ether vapor is delivered through a tube directly into the trachea a short distance from the bifurcation. A catheter about half the size of the glottis provides for the escape of expiration around it and thus the circulation of air is accomplished. A more diluted vapor is administered than is given in the intrapharyngeal method, because a sufficient volume of air or oxygen under proper pressure (15 to 20 mm. Hg) must be allowed for the respiratory needs of the patient. This provision is especially necessary to prevent the lungs from collapsing when the intrathoracic pressure is in abeyance during thoracic operations. The pressure is released at regular intervals, in order to allow the lungs to contract as in normal respiration. While this method of introducing air into the lungs may be sufficient for the maintenance of life, late observers are of the opinion that it is unsafe to continue the administration to the point of suspended respiration, for the ordinary operative routine.

Technic of Administration.—Anesthesia is induced by the ordinary drop method till the pharyngeal reflexes are abolished. With the patient lying on his back, the head is extended so that the chin is on a line with the sternum. The Jackson laryngoscope, which is fitted with a small dry battery in the handle, is passed over the upper surface and base of the tongue until the epiglottis is brought into view. A fairly firm catheter marked 26 cm. from the tip, with a side opening near the end, and about half the diameter of the glottis, is selected. This catheter, which has been lying in cold sterile water, is then passed through the laryngoscope into the glottis up to the mark, which should be even with the incisor teeth. In the normal adult patient, this reaches to within about 5 cm. of the tracheal bifurcation. The distance between the glottis and bifurcation is generally about equal to the distance between the incisor teeth and the glottis.

As the catheter passes into the trachea, there is a hissing sound. If the anesthesia is light at this point, a more or less violent attack of coughing ensues, which soon subsides, and regular breathing is resumed when the ether vapor is forced into the lungs. If the hissing sound is not heard, probably the catheter is in the esophagus instead of the trachea. When the catheter is properly placed the laryngoscope is removed, a mouth prop is inserted and the catheter attached to the tube connecting the vaporizer. From this point, the administration does not differ from the intrapharyngeal method, except that the pressure must be constantly observed and the flow interrupted three or four times a minute by pinching the tube. The respiration must also be carefully watched.

Intratracheal insufflation provides for a sufficient aëration of the lungs, regardless of the respiratory movements of the patient, and it appears when properly administered and safeguarded it can be rendered devoid of intrinsic danger. Consequently this method of anesthesia is held to be indicated in all intrathoracic work or whenever the operation may interfere in any way with voluntary respiration. Ether with air or oxygen is generally the anesthetic used; however, nitrous oxid oxygen may be combined with the ether if desired.

Dangers of Intratracheal Anesthesia.—Cotton and Boothby* call attention to the dangers of emphysema and of interference with circulation (prevention of filling of the right heart) by excessive intra-pulmonary pressure. These authors claim that a pressure in excess of 10 mm. Hg is unjustifiably dangerous. They suggest a safety valve by means of which the intrathoracic pressure cannot exceed 15 mm. Hg.

Cardinal principles to be observed in this form of administration: Guard against over-pressure which may cause rupture of the lungs and the escape of air in the cellular tissue of the neck, resulting in death; spraying of liquid ether into the lungs; introducing the tube into the esophagus or beyond the bifurcation of the trachea, trauma to the pharynx or larynx during intubation; too large a catheter which will obstruct the return flow of air; if the catheter is too far introduced, it will enter the bronchus and partly or completely occlude it, and by pressure destroy lung tissue. This may be avoided by withdrawing it and re-introducing it till it meets an obstruction which is the bifurcation, when it can again be withdrawn about an inch. A proper vaporizing apparatus, good light during the introduction of the catheter and ordinary caution should prevent these accidents. The greatest difficulty in this method of anesthesia is the introduction of the catheter into the glottis. Because of this difficulty and the inherent dangers, this method will never become a popular one. The only operations in which this method may have the advantage of the intrapharyngeal method are pulmonary operations, with exposure of both lungs to atmospheric pressure, and intestinal obstruction with more or less continuous vomiting.

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* Cotton and Boothy, Boston Med. and Surg. J., clxvi (1912), p. 468.

Eisenbrey,* writing of his experimental work on intratracheal anesthesia, remarks: "It was the writer's impression that he had heard it claimed for the method that by increasing the pressure under which the air is delivered (probably also increasing the intratracheal pressure) a condition of apnea might be produced and that with the thorax quiet and the lungs in partial distention, operations within the thorax might be performed with ease. As the results of experiments with this possibility in mind, it was found that in the intact animal such a condition could be produced, but not, however, by merely increasing machine pressure, even though it was raised to 50 mm. If the outflow remained free and no increase of intratracheal pressure resulted, no apnea developed. If, however, with a machine pressure of 15 to 20 mm. the outflow is so obstructed that an increase of intratracheal pressure of from 8 to 10 mm. was produced, the condition did occur. The fact that the cessation of respiration occurred simultaneously with a rise of intratracheal pressure and not after a period of over-ventilation that could be considered at all sufficient to produce acapnia, discourages the idea that it is an apnea due to exhaustion of CO_2. The moment the intratracheal pressure is lowered, by allowing free outflow of air from the trachea, respiration begins and the first few respiratory moments are somewhat exaggerated. It is difficult to believe that the relatively slight pressure within the lungs is sufficient to prevent respiratory efforts by mechanical fixation of the chest walls. During the quiet period, inspection does not show extreme distention of the chest. With the thorax opened, the same state of pseudo-apnea may be produced, but although respiratory movements are abolished and the lungs quiet, the pressure necessary to produce it causes a distention of the lungs to practically the full capacity of the thorax, and consequently access to the other thoracic viscera is interfered with. A very serious objection to the use of this procedure in physiologic work is the fact that marked disturbances of the circulation occur when the intra-pulmonary pressure is sufficiently raised. A pressure that is sufficient to cause cessation of respiration causes a fall in blood pressure of from 20 to 40 mm. Any lowering of the intratracheal pressure in an attempt to reduce the degree of circulatory disturbance results in a resumption of respiratory movements. If respiratory movements are not objectionable, intratracheal insufflation suffices perfectly for intrathoracic operations, and when the movements are prevented by curari, it is equally valuable, for the amount of intra-pulmonary pressure for ordinary anesthesia and for efficient artificial respiration is not sufficient to cause circulatory changes such as have been mentioned."

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* Eisenbrey, Surg., Gynec. and Obstet., xv (1912), p. 715.

Intrapharyngeal Anesthesia.—Narcosis is established in the usual manner by inhalation with the cone. A fairly firm rubber catheter, the size of which will vary with the age of the patient, is passed through the nose well into the posterior pharynx. If it is too long, there is danger of it passing into the esophagus and the vapor being forced into the stomach; on the other hand, if it does not extend through the nose, it is difficult or impossible to keep the patient asleep. If the distance between the alæ of the nose and the auditory meatus is measured on the catheter and this length passed into the nose, it will be in the proper position. The author has observed that if, in passing the catheter, it meets with a slight resistance at a certain point in its passage, it is the pharyngeal wall, and if it is introduced about 2 in. farther, it will be in proper position. The catheter should be moistened with sterile water or lubricated with some sterile oil before the introduction, otherwise there is danger of injuring the nasal mucosa. When the catheters are properly adjusted, they may be held in position by a strip of adhesive plaster across the forehead. A single catheter may be used or two catheters may be used, one for each side of the nose, and attached to the vapor tube by a "y" connection. However, many anesthetists use a single tube. The vapor may be passed through tongue depressors made for the purpose. The author has devised metal tubes of various lengths, and bent at the proper angle to direct the vapor into the posterior pharynx when placed in the angle of the mouth. These tubes have many advantages over the nasal catheter in nose, harelip and cleft-palate operations. The tube or tubes should not be introduced till the pharyngeal reflexes are abolished, otherwise the vapor will cause spasm or coughing. Should this occur, leave the catheter in position, but stop the vapor and administer more ether by the drop method.

Indications for Intrapharyngeal Anesthesia.—Any operation about the head, the nature of which prevents the use of a cone, that is, jaw, tongue or lip resection, cleft-palate, harelip, tonsils and adenoids, intra-nasal operations. On account of the necessary prone position, this method may be used to advantage in cerebellar tumor operations.

Rectal Anesthesia.—Rectal anesthesia was first employed by Pirogoff in 1847. Pure ether or ether mixed with water was introduced into the rectum. It was found that while anesthesia could be produced in this manner, the local results were disastrous. Severe pain, hemorrhagic discharges and death resulted and necropsy revealed gangrenous perforations of the cecum and general septic peritonitis. About 30 years later, ether vapor was employed instead of the liquid by Molliere. He used a bottle of ether from which a tube conveyed the vapor into the rectum. The bottle was placed in a water bath, which had a temperature greater than the boiling point of ether. The vapor was forced into the bowel by the pressure incident to its own volatile expansion. The method did not receive general favor and was abandoned. Some years later, Cunningham of Boston devised a technique which permitted the administration of ether by rectum with safety to the patient. Cunningham employed air as a vehicle for conveying the ether into the rectum. His technique was similar to the one in use at present for insufflation anesthesia. Too great pressure was prevented by the incompetence of the patient's sphincter ani or by inserting the finger into the anus, beside the tube, thus allowing the escape of the gas.

Sutton* reported a series of 140 anesthesias by this method. With one exception, the patients were first anesthetized by inhalation. Oxygen was used as a vehicle in 25; 12 received preliminary injection by morphine and scopolamin; 43 had at some time during the operation a supplementary administration by inhalation of either chloroform or ether. Twelve belched gas from the stomach in the course of the anesthesia, indicating a possible distention of the small intestines with regurgitation of the gas from the stomach; 43 cases vomited; 12 had abdominal distress; 5 had bloody stools or blood streak return from the post-anesthetic enema. The patient in the most severe case continued to pass blood for three days, during which time she vomited persistently; one developed pneumonia.

Sutton says that "enough pressure must be exerted to distend to a moderate degree the entire colon, else the available absorbing surface will be too small. Too much pressure must not be exerted, lest by overdistention the vessels of the gut be flattened out, circulation impeded or abolished and absorption mimimized and the ischemic mucosa left unprotected by its normal circulation to resist the effects of the ether." Contra-indications to this method are anal fistula or any lesion of the intestinal tract such as ulcer, because of the danger of perforation, laparotomies in general, because of the interference of the inflated colon with the surgical work. It cannot be used in emergency cases, because the lower bowel and colon must be free from all contents. This method of anesthesia has never become popular, partly because of the frequent necessity of employing inhalation anesthesia due to the difficulty of maintaining a sufficiently profound narcosis. This objection makes it prohibitive in the very cases in which it has been recommended, that is, operations about the head and neck.

Ether-oil Colonic Anesthesia.—The ether-oil colonic anesthesia has many advantages over the ether-vapor rectal anesthesia. On superficial observation the method is so simple that it has attracted the unwary. On close inspection, however, it is at once evident that it has not only distinct limitations but also distinct disadvantages. Adults are given one ounce of a 70 per cent. solution (six ounces of ether and two ounces of olive oil) for every 20 lb. of body-weight, that is, a man weighing 140 lb. would be given seven ounces. Children are given a 50 to 65 per cent. solution. The personal equation enters so largely in drug susceptibility that it would appear hazardous to attempt to figure the dosage on the basis of body-weight and age. Not to have the anesthetic under immediate control in case of untoward accident, as for example in sudden severe hemorrhage, followed by shock, is a distinct disadvantage which the merest tyro will recognize. We are told that if at any time the patient shows signs of a too profound anesthesia, a portion of the mixture should be withdrawn. While this in itself is a simple procedure, the disorder occasioned by such a necessity during a major operation must be considered. What assurance have we that the injected solution will remain in the lower bowel, especially if the operative requirements place the patient in the Trendelenburg position? If the mixture passes high in the colon or reaches the cecum, the futility of an effort to quickly recover it through lavage is evident. Inasmuch as the ether is excreted principally by the lungs, if respiratory depression develops, less ether is eliminated, while at the same time it continues to be absorbed from the rectal solution which in turn still further depresses respiration. Another objection to the method is the inability to regulate the depth of narcosis to suit the operative requirements during the different stages of the operation.

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* Sutton, Ann. Surg., li (1910), p. 457.

Reports indicate that occasionally rectal irritation, which may prove quite distressing or end in death, follows this method of etherization. Doctor Gwathmey, the originator of the method, gives the following directions.

Preliminary Treatment.—Castor oil the night before, followed in the morning by warm water enemas, one hour apart until the return is clear. The patient may then be allowed to rest for two or three hours.

One hour before the introduction of the ether mixture 5 to 20 gr. of chloretone in suppository or dissolved in 4 dr. of ether and mixed with an equal amount of olive oil are given per rectum with the patient in the Sims position. For the chloretone we may substitute 2 to 4 dr. of paraldehyd in an equal amount of olive oil.

Both the preliminary and the mixture should be administred very slowly through a funnel which is attached to the end of the catheter which has been well lubricated and inserged 4 in. into the rectum. Twenty minutes before operation a hypodermic of $\frac{1}{12}$ to $\frac{1}{4}$ gr. of morphin and $\frac{1}{200}$ to $\frac{1}{100}$ gr. of atropin is given.

The Solution.—Adults are given a mixture consisting of ether six ounces olive oil two ounces (a 75 per cent. mixture). The size of the dose is reckoned upon a basis of one ounce of the mixture to every 20 lb. of body-weight, that is, a man weighing 140 lb. would need seven ounces.

A 50 to 65 per cent. solution is sufficient for children and weak anemic adults Eight ounces of the 75 per cent. mixture will cause the anesthesia to last from two and a half to three hours. No more than eight ounces should ever be given regardless of the patient's weight.

The Administration.—With the patient in Sims position, in his own bed, the catheter (24°F.) is introduced about 4 in. into the rectum. The oil-ether mixture is then allowed to flow in, allowing at least one minute for each ounce.

The patient quickly becomes drowsy. Ether appears on the breath in from three to four minutes. Excitement may be moderate or entirely absent. After a time, 10 to 30 minutes, according to the absorptive power of the colonic mucous membrane of the patient in question, he may be placed on a stretcher and conveyed to the operating room.

The stage of maintenance is controlled by increasing or decreasing the freedom of the respiration, that is, a towel over the face will prevent the escape of the ether vapor and induce rebreathing of the expired ether causing the patient to sink into deeper narcosis. On the other hand, an artificial air-way will, by increasing the freedom of the respiration, lighten the anesthesia.

Occasionally it is necessary to supplant the rectal administration by the inhalation method using either ether or chloroform If the respiration should show signs of shallowness or failure, with cyanosis or stertor, the ether and oil injected should be immediately withdrawn by reintroducing the catheter and allowing the retained solution to run off. In the event of failure of the respiration, rebreathing of CO_2 may be beneficial. If ineffective it is recommended that a vein be opened and from 1000 to 2000 c.c. of normal saline injected with a hope of reducing the ether tension in anesthetized tissue. When the operation is well under way it has been found advisable to withdraw as much of the injection as may be reached with the catheter. At the completion of the operation a cold soap suds enema is introduced high into the colon through one tube and drawn off through the other. Two to four ounces of olive oil should be introduced and the tubes withdrawn with a view of neutralizing any ether which may remain unexcreted.

Buxton gives the following as disadvantageous in this method of narcosis: "Colicky pain in the intestine, urgent tenesmus, diarrhea, sometimes dysenteric in character, painful distention of the intestinal tract with more or less severe collapse. Deaths have been recorded."

Chloroform.—The precise action of chloroform on the mammalian organism has occupied the attention of investigators ever since the discovery of its anesthetic properties. The result of their investigations forms an invaluable working basis for all surgeons and anesthetists. The first purely physiologic research on this subject was conducted by the "Glasgow Committee" of the British Medical Association, whose report appeared in 1875. The committee found that blood pressure and cardiac action under chloroform were distinctly lowered, and that although respiration generally ceased before cardiac action did, they contended that the heart might be primarily paralyzed. This view was in harmony with that advanced by Snow, but it was opposed by the Edinburgh school, who taught that chloroform never produced primary depression of the heart. The two "Hyderabad Commissions," appointed by the Nizam, corroborated the findings of the Edinburgh school. It has been shown that there were numerous fallacies in the technical work of the Commission, and that many of the tracings on which criticism had been invited were capable of interpretations differing from those given them. The Committee of the Royal Medical and Chirurgical Society found that concentrated chloroform vapor destroyed life by arresting the heart's action, and that weak vapors considerably weakened cardiac action before death, although respiration generally ceased before circulation. They further found that very concentrated vapors caused the respiration and circulation to cease nearly simultaneously.

In 1849, Snow devised a plan by which the proportions of chloroform and air might be regulated. He employed a bag of known capacity, which was inflated by a bellows, and into this bag a measured quantity of chloroform was placed. He so regulated the proportion that a 4 per cent. vapor resulted. Since Snow's time, various administrators who have agreed with Snow as to the advantage of working with known percentage vapor have modified in various ways the apparatus originated by Snow. However perfect an apparatus may be in its mechanism, however accurately it may deliver any desirable percentage of vapor, there are certain inherent disadvantages which outweigh its advantage. The most pronounced objections to the dosimetric method of anesthesia are: The administrator's attention is directed to the apparatus, which is frequently complex in construction, rather than to the patient, who, after all, is the only true guide in anesthesia. The apparatus cannot be readily sterilized, is liable to get out of order, and can only be used in certain cases. Those that require the respiratory action of the patient to draw the current of air through them impose an added tax on the respiratory system. Recently inhalers have been invented, the principle of which is simple. Air is pumped by means of a hand or foot bellows or by an electric motor through or over the anesthetic, the air carrying with it a varying quantity of vapor which is transmitted to the patient by means of a specially constructed cone, tongue depressor, mouth tubes or nasal catheters. It is important in this system of anesthesia to see that the afferent and efferent tubes are attached to the right tubes in the bottle, otherwise some of the liquid may gain access to the efferent tube instead of the vapor.* It is impossible to state what percentage the vapor is in this method of administration. The percentage will depend principally upon the quantity of air forced over or through the anesthetic. Ever since the days of Simpson, there have been advocates of the simple open, as opposed to the complex or regulating, methods of administrating chloroform. Of all the open methods, that in which the chloroform is dropped upon a mask covered with gauze gives the best results. Depending upon the quality, six or eight layers of gauze are preferable to stockinet for the cone cover. If stockinet is used, the cone should not rest on the patient's face, as there is danger that a too concentrated vapor will be administered. A small drop can be secured by drawing the end of a cotton wick out to a fine thread. If a small drop and fairly thin cone cover are employed, a vapor varying from 1 to 3 or 4 per cent. will result, depending upon the rapidity of the dropping. The ideal to be sought for is to give continuously a well-diluted vapor.

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*Quite recently the author learned of two such accidents, one proving fatal.

Great care must be exercised if a child cries during induction. Because of deeper inhalation, an overwhelming dose may easily be administered. It is dangerous to "push" chloroform in order to more quickly secure surgical narcosis or relaxation. The general laws which apply to ether narcosis prevail in chloroform anesthesia. The respiration, circulation and pupillary reaction must be constantly watched.

In 1896, Neudorfer* of Vienna introduced a system of administering chloroform vapor and oxygen, all air being excluded during the administration. This method has been modified for the quantitative administration of chloroform vapor, oxygen and air. It is doubtful if there is any advantage in the addition of oxygen to atmospheric air during the administration of chloroform.

Chloroform should always be administered in the supine or lateral postures. Positions in which the head is raised increase cerebral anemia and the danger of syncope.

So many accidents occurred during the first years following the introduction of chloroform that many surgeons discarded it as an anesthetic and returned to ether. In the United States and particularly in the Middle West, ether has held its own from the first; but in all other parts of the world, and especially in England, chloroform is still largely used. It retained its popularity in tropical countries because ether evaporates so rapidly in high temperatures that its use is practically prohibited. It is used to a considerable extent on the battlefield where portability and convenience have to be considered.

While generally admitting that ether is very much safer than chloroform, many surgeons and anesthetists are of the opinion that the latter is comparatively difficult to administer. Many heated controversies respecting the merits of the two anesthetics have taken place. The advocates of ether urge that accidents from its use are infrequent and nearly always due to faulty administration or some pathologic condition which clearly interdicts its use. The supporters of chloroform allege that deaths following its employment often occur from surgical shock rather than from its toxic effects and that, providing the respirations are closely watched, chloroform is perfectly safe; that although ether does not, like chloroform, kill patients on the table, it does so afterwards by causing lung and kidney complications. In recent years, this ether versus chloroform question has caused many experiments to be made on animals, and through this research work, the relative safety of the two agents has been placed on a firm basis.

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* Neudorfer, Wien Med. Presse, ix (1868), p. 741.

Chloroform for anesthesia should be transparent, colorless and neutral to litmus paper. It should possess an agreeable, non-irritating odor and upon evaporation should leave no residue or strong odor. It should form no precipitate when added to a solution of silver nitrate. When heated with caustic potash, it should not turn brown. It is decomposed by light and air and therefore should be kept in colored, well-stoppered bottles. Chloroform boils between 140.2 and 141.8°F. Its density is four times that of atmospheric air. Chloroform vapor is decomposed by an open flame, forming phosgene and hydrochloric acid gases. If chloroform is administered for some time in a closed or badly ventilated room, in the presence of an open flame, gaslight, lamp, a burning oil or gas stove, the occupants of the room are liable to be affected with smarting of the eyes, a spasmodic cough, and a feeling of tightness about the chest. It is very caustic in its action on the skin, consequently care should be taken to protect the face during administration by anointing it well with cold cream or vaseline. Corneal ulcers have been known to develop from the dropping of chloroform into the eyes during administration. If this accident occurs, an immediate instillation of olive or castor oil will prevent this unfortunate complication. The necessity of keeping the lids closed and the eyes well protected with moist cotton during the administration of chloroform is obvious.

Undoubtedly chloroform is a powerful cardiac depressant producing a varying degree of dilatation of all the heart cavities. Frequently the dilatation is sudden and when extreme the heart fails, although rhythmic movements may persist for a while. Leonard Hill found that chloroform, like amyl nitrate, acts directly upon the musculature of the whole vascular system. If a dog be killed by chloroform and the chest opened, the heart will be found much dilated and exhibiting waves of contraction, although unable to empty its cavities and circulate blood through the organism. It would seem that we have in chloroform a drug which is a powerful protoplasmic poison, and when toxic quantities are introduced into the circulation a cardio-vascular paralysis quickly develops, which leads to death. If the paralysis were respiratory, artificial respiration would be successful in averting death, but because it markedly depresses circulation, the resuscitation of the patient is rendered extremely difficult. In summing up it may be said that although some still regard chloroform as a drug which reduces arterial tension and depresses respiration without interfering with cardiac action, evidence at present opposes this view in favor of the more reasonable proposition, *viz.*, that the fall of arterial tension which occurs is due to the direct effect of the anesthetic upon the heart itself; and while respiration usually ceases before the heart fails, the essential factor in the death is the effect of the anesthetic on the circulation, not on the respiration.

It is well known that the administration of chloroform may be followed by well-marked pathologic changes in the tissues, the most conspicuous being edema, fat infiltration, multiple hemorrhages and necrosis of the central portion of the liver lobules. At present, no adequate explanation as to how these changes are produced has been given. However, the process appears to be identical with those occurring in poisoning with a large group of toxic substances, including other narcotics, arsenic, salvarsan, phosphorus and possibly bacterial poisons. There is considerable evidence to show that in chloroform poisoning, the liver necrosis is produced chiefly by the action of acid (hydrochloric acid is formed in the metabolic destruction induced by chloroform). Ether does not produce necrosis. It only produces edema and fat infiltration to a less degree.

In 1866, Nothnagel* showed that the introduction of chloroform into the stomach or subcutaneous tissue of rabbits was followed by fatty degeneration of the liver, kidney and heart muscles. "Acid intoxication," "acidosis" and "delayed chloroform poisoning" are names applied to a peculiar state which is not infrequently encountered, particularly in children, after the administration of chloroform. A large amount of clinical and experimental evidence seems to prove that chloroform may bring about a peculiar toxic state within the first few days after its administration. Numerous deaths have been recorded in which the anesthetic seemed to be the sole cause of fatal symptoms arising after operation. Casper,† in 1850, expressed the belief that chloroform might produce a chronic poisoning which might end fatally after anesthesia. In the following year Langenbeck‡ reported a death which he considered due to the action of chloroform. In 1894, Guthrie§ reported a number of cases at a children's hospital in which chloroform narcosis was followed by fatal after-effects of a toxic character. The symptoms were copious, violent and persistent vomiting (the vomited matter often resembling beef-tea dregs), restlessness, loud screaming, delirium, pyrexia toward the close of life, and coma. Death usually occurred about the fifth day. Symptoms usually came on from 12 to 24 hours after the operation. The breath had a sweetish odor and the urine contained aceton and diacetic acid. Becker‖ found that acetonuria was especially liable to follow the anesthesia of children. The most noteworthy feature at post-mortem examination has been the fatty changes in the liver, heart and kidneys. In some of the cases reported the liver changes have been described as "yellow atrophy," "fatty degeneration" or "fatty infiltration." Scott, Carmichael and Beatie* reported a fatal case in which post-mortem examination showed the liver distinctly enlarged, intensely fatty and almost creamy yellow in color. When stained for fat, it was seen that all the cells from the center to the periphery of the lobule were crowded with fat globules. The kidneys and suprarenal bodies also showed fatty degeneration. The third noteworthy paper during 1905 was contributed by Bevan and Favill.† These authors describe in detail the death of a 12½ year old child which occurred in their practice, after a short chloroform anesthesia, and gave an exhaustive resumé of the literature on the subject up to that time. They were able to collect 27 fatal cases following anesthesia, making with their own 28. The patient did well for 48 hours. She then began talking incoherently and exhibited evidences of very great fright. Delirium, screaming, muscular rigidity exaggerated tendon reflexes, ankle clonus, rising pulse and temperature, moderate cyanosis and coma supervened, with death 110 hours after operation. The urine was negative before the operation, but on the third day following, it had an acidity of 11.6, contained diacetic acid, aceton, albumin, hyalin, granular and waxy casts. The breath had a sweet aceton odor. At post-mortem examination the liver was found enlarged, firm, universally yellow, with no lobular centers. Microscopically, the liver showed advanced fatty changes at the peripheries of the lobules; the central portions were congested, and the columnar arrangement of the liver cells thrown in disorder. The kidneys showed fibrous changes, the most striking change being the presence of large amounts of granular material (coagulated serum) in the cavities of the glomeruli, visibly compressing many of the tufts. The convoluted tubules were filled with a similar granular material, while the epithelial cells were well preserved. After carefully discussing the case, the conclusion was reached that the symptoms pointed to acid intoxication rather than sepsis.

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* Nothnagel, Berl. klin. Wchnschr., iii (1866), p. 31.

† Casper, Casper's Wchnsch (1850). Wchns. chr. f.d. ges. Heilk., xvi (1850), 1; 17; 33; 49.

‡ Langenbeck, Berend's "Chloroform statistics," Hanover (1850).

§ Guthrie, Lancet, i (1894), p. 193; ii (1903), p. 10; ii (1905), p. 185.

‖ Becker, Deutsch. Med. Wchnchr., xx (1894), p. 359.

Beesley‡ considers the symptoms occurring in so-called acid intoxication, acidosis, acetonuria and delayed chloroform poisoning as pointing to a metabolic disturbance in the organism, one of the ultimate products of which is aceton. He examined the urine of a large number of children at the Royal Hospital for Sick Children before and after anesthesia, and found that both ether and chloroform produced a temporary acute acetonuria, but that if acetonuria were present before operation, chloroform proved to be far more dangerous than ether. Thus of 19 cases in which operation was performed under chloroform no less than 14 patients died, all exhibiting symptoms of acid intoxication or aceton poisoning. Post-mortem examination showed the usual fatty degeneration. Of 24 patients operated upon under ether, only two died and not as a result of acid intoxication. The most recent contribution to this subject is by Evarts A. Graham.§

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* Carmichael and Beatie, Lancet, ii (1905), p. 437.

† Bevan and Favill, J. A. M. A., xlv (1905), p. 754.

‡ Beesley, Brit. Med. J., i (1906), p. 1142.

§ Graham, J. Exper. Med., xv (1912), p. 307.

In this author's study of the diseases of the newborn that are characterized by hemorrhagic tendency, icterus and fatty infiltration of the viscera, he found that "when pregnant animals were chloroformed, their offspring showed changes characteristic of the pathologic and clinical pictures of the various hemorrhagic diseases of the newborn,'' and that "there is evidence strongly suggestive that primarily all are manifestations of an insufficient supply of available oxygen in the tissues" . . . therefore it would seem, a priori, that there is some evidence to suggest the existence of a causal relationship between chloroform used at labor and the occurrence of some of these various conditions in the newborn. In order to investigate further this possibility, experiments were devised with the object of answering the following questions: (1) Will chloroform when given in amounts small enough to be comparable to that ordinarily used in labor produce any anatomical lesions in the young? (2) When given at or near the time of labor, can conditions be produced resembling clinically any or all of the affections of the newborn under discussion?

The experimental results may be summarized briefly as follows:

When chloroform was administered to pregnant animals near term in two or three overwhelming doses, at intervals of only a day or two, it was followed by the intra-uterine death of the fetus, with pathologic pictures characterized chiefly by visceral fatty changes and slight icterus. In most of the experiments the mother also died, showing a similar picture.

When given an amount small enough to produce anesthesia for only 10 or 15 minutes in the pregnant animal, which is comparable to the amount frequently given to women in labor, it was followed by intra-uterine death of the young and abortion and very definite fatty changes in the liver of the offspring.

With a very light anesthesia of a few minutes, the young have been born apparently in good health, have remained so for a few days, but have generally succumbed during the first week, with pictures sometimes resembling Buhl's, sometimes Winckel's disease." "These changes, however, may follow the administration of any substance that can cause tissue asphyxia with attendant accumulation of organic acid." Graham, working upon the hypothesis that the necrosis was chiefly the effect of acid, administered an alkali simultaneously with the chloroform, and noted accordingly that the liver necrosis was either entirely prevented or greatly inhibited. He found that in the control animals which received no alkali the kidneys were always enormously swollen and weighed much more than those of the alkalinized animals. "Acid gives rise to asphyxia and asphyxia gives rise to acid production. In this connection, the location of the necrosis in the central part of the lobule is of interest, for this is the region which is farthest removed from the oxygen supply and from compensatory influence carried in by the blood. It is also farthest removed from the neutralizing effect of alkalies brought in by the blood. Ether does not produce necrosis. It induces only edema and fat infiltration to a less marked degree."

Renal Function under Chloroform.—During full anesthesia, the urinary output is always diminished and may even be suppressed. Many observers* believe that chloroform is more damaging to the renal epithelium than ether, as is evidenced by the more persistent presence of albumin and casts in the urine after the administration of chloroform.

Ether.—Ether, otherwise known as ethyl oxid, ethylic ether, sulphuric ether or simply ether, has a chemical formula $(C_2H_5)_2O$. It was first prepared by Valerius Corders† in 1540, who gave it the name of "Oleum Vitroli dulce." It is a transparent, highly volatile liquid, possessing a characteristic pungent odor and burning taste. It boils at a temperature of 96°F. under the ordinary atmospheric pressure. Ether is miscible with alcohol and chloroform and soluble in water to the extent of 10 per cent. It is eliminated from the system chiefly by the lungs and in small part by the kidneys and gastro-intestinal tract and escapes from the body unchanged. It causes a rise of arterial pressure by stimulating the vasomotor center and also by stimulating the heart. In moderate amounts it increases the force and frequency of the pulse by its effect on the heart muscle. Large doses act as a cardiac depressant, especially if there is an accumulation of CO_2 with a consequent anoxemia. Poisonous doses produce death by paralysis of the respiratory center. It is decomposed by light and air and therefore should be kept in well-stoppered cans or dark bottles. It is highly inflammable, burning with a white luminous flame.

T. L. Deavor‡ and L. F. Schmauss,§ investigated the inflammability of ether, both liquid and vapor, in the presence of an open flame or actual cautery. Their experimental findings are interesting and instructive. A red-hot iron plunged into a can of ether produces a penetrating gas, like formaldehyd, but does not ignite the ether. Ether in an open vessel is set afire more readily than alcohol or gasoline; however, the flames must be brought to within an inch or two of the liquid. Ether in a can will ignite and burn with a small flame, which will gradually die out without exploding. Only when enough oxygen is furnished to give complete combustion is sufficient heat produced with the resulting expansion of air to cause an explosion. Ether vapor is two and a half times heavier than air, and consequently does not rise very high above the level at which it is generated. Because of the weight and density, the vapor rapidly settles on the nearest surface. The smoother the material—porcelain, glass, wood—the more rapidly the vapor follows it, and spreads in all directions, and if ignited will burn over a considerable surface. If ether and water are well shaken together, the ether will burn as freely as before until exhausted. If water is dashed on burning ether, it will displace the ether in many directions and simply scatter the fire and alarmingly increase the conflagration. Likewise a burning ether sponge or cotton kicked or flung across the room or stamped on will widely distribute the fire in small quantities, or cling to the shoe and may set fire to clothing of the physician or nurse or be carried from place to place about the room. An open flame, gas jet, high frequency spark or actual cautery should not be permitted within 3 ft. of the mask during etherization of a patient, and by no means if a table or other unobstructed surface intervenes between the flame and the mask. If the vapor should ignite, the flame should be quickly and methodically smothered, beginning at the patient's face, as ether exhaled by the patient is inflammable.

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* Many observers, etc., Lancet, ii (1905), p. 1920.

† Corders, Valerius, Watts' "Dictionary of chemistry," ii, p. 464.

‡ Deaver, Am. J. Surg., xxix (1915), p. 286.

§ Schmauss, J. Ind. Med. Assn. vii (1914), 559.

The author once witnessed such an accident, when the actual cautery was used for a throat condition following an etherization. The sheet covering the patient was quickly seized and clapped over the mouth and the flames extinguished before any evil consequences resulted. However, the experience was a thrilling one.

Accidents have been reported in which the spark from the *x*-ray apparatus has ignited ether vapor while patients were under examination or operation. As children must frequently be rayed under anesthesia to secure quiet, due precaution should be taken.

Impurities.—Pure ethylic ether should be neutral to litmus paper and should evaporate without leaving a distinct or foul smelling residue. It should form a clear mixture in any proportion with oil of copaiba. Potassium sulphate is insoluble in anhydrous ether, but is slightly soluble in ether containing water, a brown residue developing. For further tests, the reader is referred to Watt's "Dictionary of Chemistry," second Supplement, 1875, article "Ethyl Oxid."

Contrary to chloroform, ether is one of the most energetic stimulants known to the respiratory and circulatory systems.

Ringer* found that one or two minims of chloroform arrested the ventricles of the frog's heart and that 50 minims of ether simply accelerated and slightly weakened the beats.

Fleming,† in a review of inquests held in England, showed that out of 700 deaths occurring during anesthesia, 521 were due to the anesthetic. Of these patients, 223 died before the operation was begun. His statistics are interesting and instructive.

Chloroform	378
Ether	28
C. E. A. C. E. and A. C.	100
Nitrous oxid	12
Ethyl chlorid	6
Spinal	8
Scopolamin	2
Hedonal	2
Local	6
Not specified	158

In analyzing these figures, one is at once impressed with the dominance of fatalities under chloroform and it is difficult not to attribute them to the improper anesthetic agent, although the inexperience of the administrators may have been a contributing factor. Fleming is undoubtedly correct in his belief that this appalling death-rate would not have occurred if ether had been administered instead of chloroform. From a purely scientific point of view, these statistics serve to show the great need of reform in the selection and administration of anesthetics.

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* Ringer, Practitioner, xxvi (1881), p. 436.

† Fleming, Proc. Roy. Soc. Med., Anesthesia Sec., vii (1914), p. 17.

Ether is more potent than nitrous oxid and less potent than chloroform. By reason of its low boiling point (96°F.) it is quickly eliminated from the body when the administration is discontinued. The phenomena of anesthesia will greatly depend upon the method of administration and the extent to which air is limited.

Any ether which forms snow on the cork or wick when left standing or which freezes on the cone cover during administration should be discarded as being unsuitable for the open method of anesthesia. With such an ether, it is difficult, often impossible, to maintain an even smooth anesthesia and, furthermore, a much larger quantity is required, which offsets the difference in price.

Temperature of the Ether Vapor.—That there is any advantage in warming ether vapor to body temperature has been questioned by such able observers as Sellig,[*] Meltzer,[†] Cotlon and Boothby,[‡] Bevan,[§] McCarthy and Davis,[||] and others. Sellig says: "Despite the fact that ether vapor was driven through a temperature approximating 100°C., it radiated its acquired heat so rapidly that at a distance of one meter from the source of heat it had practically assumed room temperature." McCarthy and Davis, using dogs, carried on a series of investigations on the use of warmed ether vapor for anesthesia. They found that the most satisfactory method of warming the ether was to heat the vaporized ether by passing it through a coil of tubing immersed in boiling water. They say: "In the intrapharyngeal methods the vapor was first passed through a jar containing a thermometer bulb to record the temperature at delivery to the patient and from this it was passed into a catheter which was inserted in the first instance through the nares into the pharynx, and in the latter through the mouth directly into the trachea. By placing a thermometer in the trachea or in the pharynx through a high tracheotomy incision, as the case might require, we were enabled to determine the temperature of the vapor at the point of delivery in the pharynx or the trachea, and furthermore, it became possible to estimate the efficiency of the various parts of the respiratory tract as heating chambers. As a check on this method the intubing catheter was carried out through a tracheotomy incision directly into a bottle which was provided with a thermometer and inlet and outlet tubes. As a further check, lengths of tubing equivalent to those used intrapharyngeally and intratracheally were inclosed in an incubator at 37.5°C., and the change in

[*] Sellig, Interstate Med. J., xviii (1911), p. 927.

[†] Meltzer, N. Y. Med. Rec., lxxvii (1910), p. 477.

[‡] Cotton and Boothby, Surg., Gynec. and Obstet., xv (1912), p. 724.

[§] Bevan, J. A. M. A., lxv (1915), p. 1418.

[||] McCarthy and Davis, Ann. Surg., lxiii (1916), p. 305.

temperature of the vapor recorded as it passed through this tubing at the same rate as it had been passed into the trachea. The degree of warming of the vapor corresponds closely in this artificial respiratory tract to that observed in the dog. Before concluding the intrapharyngeal experiments, the main bronchus of the lower lobe of one lung was opened, a thermometer inserted and the temperature of the vapor at that level recorded." These authors conclude: "When ether is administered by inhalation, unwarmed, the vapor reaches the middle of the trachea at a temperature within one or two degrees of body temperature. In intrapharyngeal insufflation, where the warming effect of the mouth is partly lost, the temperature in the trachea is three or four degrees below body temperature. It is safe to assume, however, that in both instances the temperature is increased to that of the body before the vapor has passed through the primary bronchi. When the unheated vapor is delivered through a catheter inserted nearly to the tracheal bifurcation, it is delivered considerably below body temperature, about 14 degrees; but of this deficiency, 10 degrees have been added by the time the primary bronchus is past, so that the vapor unquestionably has been warmed to body temperature long before it reaches the alveoli."

McCarthy and Davis call attention to the fallacy of the contention that ether vapor warmed to body temperature is less irritating to mucous membranes than the unheated vapor, or that it conserves the energy of the patient by lessening the elimination of heat by the lungs which would be required to warm the vapor. They also have found that the maintenance of surgical anesthesia required the same degree of concentration, approximately 6 per cent., of the warmed or unwarmed vapor. This agrees with Connell's findings.

The advocates of warming ether vapor have overlooked the fact that nature has carefully protected the lung alveoli by placing between them and the external air, a long passage through which air must pass before reaching them. During the transit, the air is warmed to body temperature. Were this not true, it is doubtful if warm blooded animals could exist in the polar regions. Of much greater importance than warming the ether vapor is the conservation of the body heat during anesthesia. Vierdordt* gives 11 calories per hour as the normal elimination of heat by the lungs, and 90 calories by the skin. When these figures are contrasted, the necessity of preventing the loss of heat by the skin through radiation, evaporation, or conduction is apparent. Boothby says: "From a calculation of the loss of heat directly attributable to warming anesthetic vapors, it is demonstrated that such a loss is negligible in comparison to that from the body surface." Loss of heat is probably due to dilatation of cutaneous vessels rather than to a disturbance of the heat regulating center or lessened heat production from diminished muscular movements, because the loss of heat can be prevented by covering, or even raised above normal if the patient is surrounded by hot-water bottles. The loss of heat is greater when morphin has been administered before anesthesia and is greatest when a considerable portion of the body is exposed or covered by wet clothing. Dudley P. Allen* calls attention to the possible dangers of high temperature in operating rooms. He says: "In a room having a temperature of 93 to 96°F., the dog's temperature was increased very greatly under anesthesia, that is, from 4° to 6°F. At the same time, the blood pressure increased. The dog panted violently and was wet with perspiration and seemed greatly exhausted at the close of the experiment." Allen further remarks: "This observation fairly raises the question if operations under high temperatures are not exhausting to the patient as well as to the operator, and distinctly less advantageous than operations in a room of moderate temperature with the patient well protected." After the completion of the operation, a fresh gown and woolen covering should be placed on the patient for the journey back to his room. It is a well-known fact that pneumonia frequently develops in a robust person after an exposure to cold and wet. We all harbor the organisms of pneumonia and all that is necessary for the development of the affection is a lowered vitality. The question naturally arises whether many of the post-operative pneumonias might not be prevented if greater care were exercised in preventing loss of body heat during and following operations.

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* Vierdordt, Daten and Tabellen für Mediziner.

In vaporizing ether, there is an advantage in warming the liquid ether, not because of any value in warm vapor, but because when air is forced over or through liquid ether, the warm ether vaporizes more rapidly and consequently less air is required to carry the same amount of ether.

Nitrous Oxid.—Nitrous oxid (N_2O) was discovered by Priestly in 1772. It is a colorless, sweetish smelling, transparent gas, of specific gravity 1.5. It was first liquefied by Faraday in 1823. To maintain it in the liquid state requires a pressure of 50 atmospheres at 44.6°F. It is supplied in steel cylinders, made to withstand a pressure of 220 atmospheres in order to provide for increased expansion force produced by higher surrounding temperatures. Fifteen ounces by weight of the liquid will make approximately 50 gal. of gas. The cylinders should be kept away from sources of heat, such as radiators, stoves, etc., as there is some danger of exploding; likewise they should not be dropped upon hard surfaces such as tiled floors.

In 1799, Sir Humphrey Davy reported the result of his investigation of nitrous oxid. He believed that during its passage through the circulation, it was decomposed into its constituent elements, and he described the anesthetic properties of the gas to hyper-oxygenation of the blood.

Herman† came to the conclusion that it was not altered in its passage through the blood, that it was simply absorbed by the plasma without producing any change in the blood itself.

* Allen, Am. J. Med. Sci. (1897), p. 298. cxii.

† Herman, Brit. Med. J. (Apr. 18, 1868), p. 378.

Other observers maintained that the anesthetic effects of nitrous oxid were due to the lack of oxygen or an asphyxial element, till Andrews* demonstrated the fact that nitrous oxid and oxygen combined produced a much more satisfactory anesthesia than nitrous oxid alone. Ten years later, Paul Bert placed on a scientific basis the claims which Andrews had advanced.

It is now generally admitted that the phenomena which attends the administration of pure nitrous oxid are asphyxial symptoms which can be controlled or produced by increasing or diminishing the percentage of oxygen allowed with the gas. Many observers now consider the asphyxial phenomena as incidental to faulty administration, and unnecessary in the production of narcosis. Anesthesia develops when as much oxygen (20 per cent.) is administered with the nitrous oxid as is present in atmospheric air. Necropsies on subjects who have died while under the influence of nitrous oxid show the usual signs of asphyxia, the right heart cavities being full and the left comparatively empty. When death takes place, the heart continues to beat, in some cases for several minutes, after respiration ceases. The respiratory arrest is due to muscular spasm and not to a central paralysis.

Blood Pressure.—Kemp† found that blood pressure under pure nitrous oxid is markedly raised. The results which he obtained paralleled those observed in asphyxia.

McKesson‡ says: "It has been erroneously claimed that nitrous-oxid-oxygen increases blood pressure, at least this is not true clinically. However, these gases may be administered in any operation which is comparatively free from ether shock-producing factors for two hours without a material change in either diastolic or systoltic pressure, but there is a time limit beyond which blood pressure will progressively fall even under nitrous-oxid-oxygen, but, differing from ether, this fall is discontinued at once upon removing the anesthetic, and is followed by a comparatively rapid rise, approaching the normal pressure within a few minutes." This data was obtained during prolonged administration for the relief of gallstone colic and eclamptic seizures. The success in the administration of nitrous oxid and oxygen largely depends upon the perfect working of the apparatus and the accuracy with which the face-piece fits. If the face-piece fits accurately, a sound will be produced by the acting valves by which the administrator will know that air is not entering around the sides of the cone.

There is no economy in the purchase of cheap forms of apparatus, for they necessitate not only a constant expense in necessary repairs but usually a waste of gas through leakage aside from the destruction of the morale of the anesthetist and surgeon. When the gas apparatus is not equipped with a reducing valve and there has been a constant flow of nitrous oxid for some time, the intense cold produced by the change from the liquid to the gaseous state frequently freezes the valves and prevents the flow of gas. If such a valve is widely opened, the sudden pressure of the gas will sometimes blow away the obstruction. If a hot-water bag is laid on the cylinder, freezing will not occur. With a properly working apparatus, unconsciousness comes on so quickly that the patient hardly has time to sense the odor or define his feelings. When the gas is pure and properly administered, symptoms of excitement do not occur. Dreams are common but usually indistinctly remembered. When they can be recalled, they are nearly always of a pleasant nature and the patient regrets having been disturbed, and for the moment forgets where he is or that an operation has been performed.

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* Andrews, Brit. Dental Sci. (Sept., 1868), p. 485; *Ibid*. (1869), p. 22.

† Kemp, Brit. Med. J., ii (1897), p. 1480.

‡ McKesson, "Year-book of anaesthesia and analgesia" (1915), p. 91.

When a child is old enough to be taught to breathe through the nose while the mouth is open, the administration may be conducted with the nasal inhaler for operations within the mouth. If this plan is not feasible, the regular inhaler may be changed for a gag, tongue depressor or tube through which the gas can be carried to the pharynx. As anesthesia develops, the skin loses its normal color and duskiness soon appears, which passes into lividity with clonic muscular contractions if the oxygen supply is too greatly limited. Diffuse epileptiform seizures, the so-called "jactitations," is an intercurrent condition, is due to want of oxygen, and is neither an essential nor desirable feature in true nitrous oxid and oxygen anesthesia. It is an asphyxiation and should not be permitted to exist, because it is the forerunner of respiratory cessation. Stertor, anoxemia, convulsions and lividity quickly disappear when more oxygen is allowed or the cone is removed. As anesthesia advances, the heart action becomes accelerated, and as it increases in frequency the pulse loses to a considerable extent its previous fullness. With the admission of air or oxygen, the pulse abruptly becomes slower and fuller. The analgesia following a single administration, is about 30 seconds, and is known as the "available anesthesia." The period of the so-called available anesthesia is, to a considerable extent, dependent upon the length of the administrations, a long anesthesia being generally followed by a longer analgesia. During the early stages of induction, any attempt to raise the upper eyelid will cause a reflex tightening of the orbicularis muscle. This passes in a few moments and the lid may be raised without resistance. The next step will be a rolling of the globe or a slight oscillary movement, the pupil becoming dilated and anesthesia is now present. A tranquil and immobile state can usually be maintained by keeping the skin a shade dusky. Complete muscular relaxation cannot be expected with nitrous oxid and oxygen. However, greater relaxation will be secured if anoxemia is avoided. It is the custom of the author to be guided in the degree of narcosis by eye findings and the color of the patient, regardless of the percentage of oxygen being administered. A patient should never be allowed to become cyanotic. The majority can be held under anesthesia with almost normal color. As with all anesthetics, the patient is the oxygen index and not the apparatus used for delivering the gases. Weakly, anemic subjects and children bear oxygen limitation badly; therefore, high percentage of oxygen (20 to 40 per cent. or more, depending upon the color) may be allowed, with a resulting quiet anesthesia.

Dangers Connected with the Administration of Nitrous Oxid.—From the physiologic and clinical facts, it is clear that nitrous oxid in its pure state is respirable only up to a certain point. When this point has been reached, oxygen must be admitted, otherwise respiration will cease. When all air or oxygen is rigidly excluded and pure nitrous oxid enters the lungs with each respiration, asphyxial phenomena rapidly supervene. When to-and-fro or rebreathing administration methods are practiced instead of the excreted carbonic acid escaping, as it ordinarily does through the valvular opening in the inhaler, it is expired into the inhaling bag. The quantity will progressively increase within the bag as long as to-and-fro breathing is permitted. The quality of the respiratory product in the bag will depend upon the amount of air or oxygen that has been admitted with the nitrous oxid.

Anesthetic Mixtures.—A large number of mixtures of various anesthetics have been recommended from time to time. They are much more popular in England and Europe than they are in this country. The most common is the so-called A. C. E. mixture, composed of alcohol one part, chloroform two parts, and ether three parts, or some modification of it, as the Bilroth mixture, composed of one part alcohol, three parts of chloroform and one of ether, or the Vienna mixture, consisting of one part chloroform and three of ether.

It was supposed that the alcohol antagonized any depression produced by the anesthetic, increased the stupefying effects of the ether and chloroform and also prevented a too concentrated chloroform vapor from being respired, thereby counteracting any tendency to circulatory depression. A better knowledge of the physiologic action of alcohol has proved the idea to be fallacious. The number of accidents under the use of this mixture is very considerable and they are by no means as safe as ether alone, although perhaps less dangerous than chloroform alone.

The objection to these mixtures is that the constituents have not the same rate of vaporization. The more volatile agent will first vaporize, leaving the less volatile to be subsequently respired. Further, the more volatile the anesthetic, the less will be absorbed by the blood in a given time and the more rapid will be its elimination. Chloroform has a high boiling point and consequently is rapidly absorbed and slowly eliminated, owing to the temperature of the blood being below such evaporation point, while the contrary is true of ether. The A. C. E. mixture has given results very similar to those of chloroform, especially when the supply of air has been limited.

Ethyl Chlorid.—Ethyl chlorid (C_2H_5Cl) was discovered by Florens in 1847. It is a colorless liquid, with an odor somewhat like that of chloroform. The density of its vapor approaches that of ether, being 2.2 as compared with air. It boils at a temperature of 12.5°C.

It is highly volatile and consequently is kept in sealed glass tubes, which contain 2, 3, 5 c.c. or more which will keep indefinitely. The effects produced by ethyl chlorid come about very quickly, consciousness being lost in a remarkably short time, within a few seconds. In this it resembles nitrous oxid in the rapidity with which it abolishes consciousness and, on the other hand, it is like chloroform, in the suddenness with which it destroys life when administered in an overdose. Children and alcoholics appear to be especially susceptible. It may be administered by spraying it inside of the cone or on the gauze of the vaporizing chamber of the inhaler. However, better results appear to be obtained by the closed system, the ethyl chlorid being placed in a bag, into and out of which the patient breathes. The quantity required to produce anesthesia will depend upon the age, characteristics, and general physique of the subject, the method by which the drug is given and the extent to which air is permitted to dilute the vapor. Like nitrous oxide, a comparatively small quantity will produce a powerful effect if the air is restricted and rebreathing be freely employed. If the inhaler with a bag is used, 1 or 2 c.c. will usually be sufficient to produce anesthesia in children and 2 to 3 c.c. will anesthetize most adults, but 4 to 5 c.c. may be required for very strong men. When administered by the closed method anesthesia is produced in a few seconds. An important point to remember is that anesthesia may deepen after the removal of the inhaling apparatus, due to the continued absorption of the vapor from the lower air passages. This is particularly true in children, especially if there is any obstruction to breathing, hence the danger of its use in hypertrophied tonsil and adenoid patients. Narcosis is so rapidly induced that it is difficult or impossible to recognize any stage or degree in the administration. After a few breaths, when the vapor has been gradually administered, there may be a moment of exhilaration and consciousness is suddenly lost. Occasionally a short period of struggling with muscular rigidity and opisthotonos occurs. If stertorous respiration develops the administration should be stopped or more air allowed. When used as a preliminary to ether anesthesia, it is advisable to slowly add the ether while still administering the ethyl chlorid, as is practiced in the nitrous-oxid-oxygen-ether sequence. Generally speaking, the length of an available anesthesia is a little longer than the duration of the administration. Should a longer anesthesia be desired, more of the drug must be added. However, it seems to be universally recognized that ethyl chlorid is unsuitable for prolonged operations. A continuous administration is preferable to repeated administrations, except in dental operation, when it is not possible to keep the mouth and throat free from blood with the aspirator.

Similar to nitrous oxid, it may be administered with a small nasal inhaler, which leaves the mouth uncovered for operative procedure. The use of ethyl chlorid has been practically restricted to short operations or incomplete narcosis (talking anesthesia) or as a preliminary to ether anesthesia. The margin of safety is too small between the stage of surgical anesthesia (muscular relaxation) and a lethal dose for its employment as a general anesthetic agent. It has been quite extensively employed by dentists for extraction, opening abscesses, preparing sensitive cavities and removing pulps. Headaches, nausea and vomiting are more apt to follow the administration of ethyl chlorid than nitrous oxid, its advantage over nitrous oxid being that it is more easily portable and requires no special apparatus for its administration. On the other hand, nitrous-oxid-oxygen may be administered continuously for hours without any untoward effects. There has been a considerable diminution rather than an extension recently in the use of ethyl chlorid, due to the numerous accidents that have occurred under its influence. There is good reason to believe that the risk attending its administration is considerably greater than was at first supposed. Authorities are now quite generally of the opinion that ethyl chlorid is as dangerous as chloroform if not more so. Statistics would seem to prove that its mortality rate is from 1:2000 to 1:3000. Lee's report based on 5575 administrations in the Pennsylvania Hospital shows five deaths, a mortality of about 1:1000. Small doses may increase the force of respiration and raise blood pressure. Large doses depress both functions, producing an irregular pulse and rapid respiration. Death is due to respiratory failure which precedes cardiac failure.

The color of the patient does not change during full narcosis, consequently it can be readily seen that the limit of safety may be overstepped and the patient plunged into a dangerously deep degree of narcosis without any warning symptom. It is far more dangerous than ether or nitrous oxid. Its administration is especially dangerous as a preliminary to chloroform anesthesia because both drugs markedly depress the circulation. It is necessary to be cautious in recommending ethyl chlorid for general anesthesia.

Ethyl Bromid.—Ethyl bromid was first prepared by Serullas in 1827. It is a transparent, colorless, volatile liquid, of a sweetish odor and pungent taste. In 1849 Nunnelen of Leeds suggested ethyl bromid as a general anesthesia. When administered with a closed inhaler anesthesia is produced in about 60 seconds and recovery is correspondingly speedy. A dram or 1½ dr. is placed in the inhaler and little or no air admitted for the first few inhalations, after which the air cap of the apparatus may be opened. Ethyl bromid is decomposed by air and light and therefore should be kept in hermetically sealed dark-colored bottles in a dark place. Ethyl bromid has the same physiologic effects as ethyl chlorid.

It has been suggested that some of the accidents which have occurred under its use were due to the substitution of ethylene bromid or to the employment of ethyl bromid which had undergone chemical change. It does not produce muscular relaxation unless the anesthesia is very profound. The accidents which have been reported under its use have been sudden early cardiac failure and respiratory paralysis. It has never been employed to a very great extent; however, sufficient statistics have been collected to indicate that it is more dangerous than chloroform. As compared with nitrous oxid it is distinctly inferior, not only in point of safety, but in the greater liability to unpleasant after-effects, as headaches and nausea.

Ethylene.—"During the early part of 1908* severe losses were sustained by carnation growers shipping their product into Chicago, because of the fact that these flowers, when placed in the greenhouses, would 'go to sleep,' whereas the buds already showing petals failed to open. Crocker and Knight† of the Hull Botanical Laboratory undertook the study of the effect of illuminating gas on flowering carnations the result of which showed that ethylene, which forms approximately 4 per cent. of the gas, is the chief constituent that determines the toxicity of the gas for plants. Their investigations showed that 1 part of ethylene in 2,000,000 parts of air caused the already opened flowers to close, on 12 hours' exposure, whereas 1 part in 1,000,000 prevented the opening of buds already showing petals.

"Because of its marked toxic effects on flowering carnations and plants, the question of the toxicity of ethylene for animals naturally arose. The extreme toxicity of ethylene for plants furthermore suggested the possibility that some of the toxic properties of ordinary illuminating gas for animals might be due to its ethylene rather than to its carbon monoxide content. Several experiments having been performed with various concentrations of ethylene with no perceptible toxic, but, if anything, mildly anesthetizing effects, it was decided to use higher concentrations. The animals used for these experiments were successively frogs, white mice, white rats, guinea pigs, rabbits, kittens, dogs and man." It was found that all of these animals could be anesthetized with a 90 per cent. ethylene mixture in one-half the time necessary to anesthetize the same animals with the same percentage of nitrous oxid, furthermore no deleterious after affects occurred.

As these investigators had carried their investigations as far as was possible in a laboratory, a demonstration was made before a group of surgeons and professional anesthetists with the result that three days later the author, on March 14, 1923, administered ethylene and Arthur Dean Bevan operated on three patients. All precautions were taken to give the gas a fair and adequate trial and consequently at first patients who were in good physical condition requiring minor operations were selected. As we became familiar with the method of administration, the signs of anesthesia and the affect on respiration and circulation, its use was extended to handicapped patients who required major operative interference. It has been administered without any evil after effects to patients suffering with severe myocarditis, auricular fibrillation, severe valvular heart lesions, aneurism of the aorta, marked artero-sclerosis with high blood pressure, diabetes, acute and chronic respiratory infections, emphysema, various kidney infections and acute and chronic nephritis. No change was observed in the urinary findings, or blood chemistry.

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* Luckhardt and Carter, J. A. M. A., lxxx (1923), p 765.

† Bot. Gaz. xlvi (1908), p. 259.

On account of the low boiling point (157°F.) ethylene is rapidly eliminated from the tissues consequently consciousness quickly returns after the administration ceases, although analgesia may remain for a short time (one to two minutes). The interesting fact has been demonstrated that analgesia may occur while consciousness is present. Ethylene-oxygen produces muscular relaxation almost equal to ether. Operations requiring muscular relaxation should not be started till narcosis is well established as relaxation is progressive and usually reaches its maximum in from 6 to 12 minutes after the beginning of the administration.

The signs of anesthesia parallel very closely those of nitrous oxid-oxygen. When no premedication has been given the following eye signs may be depended upon: Any resistance to raising the lid indicates a very light anesthesia. The most desirable condition and one that is free from asphyxial dangers is when the lid is relaxed and the eyeball slowly oscillates, however if the eyeball is stationary with the pupil looking straight forward and with an active light reflex, safety is still present. If the eyeball is turned and fixed (eccentric pupil) chronic muscular spasms will soon develop and unless more oxygen is immediately given death will occur. It must be remembered that death from ethylene like death from nitrous oxid-oxygen is due to an insufficient amount of oxygen. Postmortem the right heart is found full of blood while the left heart is empty, which corresponds to the condition found in death from suffocation.

Respiration.—As is the rule with all anesthetic agents the breathing during the induction period is a voluntery act and consequently the attitude of the patient plays an important rôle, however, it may be stated that unconsciousness occurs so quickly, especially in young, crying children that great care must be taken to allow high percentages of oxygen in order to avoid asphyxia. The fact must be emphasized that the younger the child the more oxygen must be given or an asphyxial death may occur just as in the administration of nitrous oxid. When narcosis is established and sufficient oxygen administered to prevent cyanosis the breathing becomes almost machine like in its rate, depth and regularity. As ethylene is devoid of all irritating properties it may safely be administered in acute and chronic respiratory affections.

Heart Action and Blood Pressure.—When narcosis is established and all asphyxial indications are avoided the pulse and blood pressure remain practically normal for that individual. Ethylene *per se* will not *produce* shock neither will it *prevent* traumatic shock (hemorrhage at field of operation, rough handling of sensitive or inflammed tissues, etc.).

Inflammability.—As ethylene is an inflammable gas, like ether, it should not be used in the presence of a cautery, open flame, or any sort of electrical apparatus capable of producing a spark. It forms with air or oxygen an explosive mixture in a concentration of 4 volumes of ethylene with 96 volumes of air.

In a communication from the Bureau of Explosives for the United States and Canada, the range of explosive mixtures for ether and for ethylene when mixed with air is given as follows:

Ether Vapor	2.9% to 7.5%
Ethylene	4.2% to 14.5%

From the Bureau of Standards at Washington the following percentages mixed with air are regarded as combustible:

Ether	1.7% to 48%
Ethylene	3.3% to 25.6%

From these figures it would seem that ethylene as used for anesthesia is safer than ether. It is well to remember that oxygen supports combustion and consequently the danger is greater when large percentages of oxygen are being used.

Degrees of Anesthesia.—By carefully studying the effects produced by anesthetics, it has been possible to speak of the depth, degree or the stage of narcosis. In a general sense, three stages may be recognized: The stage of light anesthesia, the stage of deep anesthesia and the stage of paralysis or death. The depth or degree of narcosis may be known by the pupillary reaction to light.

When patients have been given no hypnotic drug as a preliminary to anesthesia, the pupillary reaction is the most valuable guide that the administrator has to the depth or degree of narcosis. Dilatation from operative stimuli is transient and need not be confounded with that produced by the anesthetic. A dilated pupil which reacts quickly to light indicates a light anesthesia. A dilated pupil which reacts slowly to light means a profound anesthesia. A pupil which is widely dilated and does not react to light shows a dangerously deep anesthesia, and respiratory paralysis is at hand. A contracted pupil indicates a moderate degree of anesthesia. In testing the pupillary reaction, the amount of light which strikes the pupil must be taken into account. Naturally if the light is dull, the reaction will not be so active. When elevating the lid, the finger should be gently but firmly pressed close to the margin, and the lid suddenly raised. If the lid is slowly brought up and the narcosis is very light, the reaction may be lost. When there is any resistance to manipulating the lid, the anesthesia is very light, too light for operative work.

The depth or degree of narcosis must correspond to the operative requirements. Different operations and different periods of the same operation require different degrees of anesthesia. Generally speaking, patients in good condition may be safely kept in a state of deep narcosis. The accompaniments of a light anesthesia in intra-abdominal operations are frequently a severe handicap to the surgeon, sometimes making the completion of the operation well-nigh impossible. In young infants and feeble children a very important task devolves upon the anesthetist, that of securing muscular relaxation on the one hand, and that of safely steering the patient through the deeper levels of anesthesia on the other. Robust patients are more apt than weakly subjects to exhibit reflex phenomena in response to intra-abdominal stimuli. Intra-abdominal operations have a special interest for the anesthetist in that they frequently produce reflex respiratory and circulatory phenomena. The modification may be very marked or so slight as to escape attention. It may manifest itself during light or the most profound narcosis. Manipulations within the upper part of the abdominal cavity in the gall-bladder region have a tendency to bring about a characteristic expiratory "grunt." Manipulation in the neighborhood of the solar plexus, traction on the omentum and similar procedures may cause sudden circulatory depression, the symptoms of which are likely to be erroneously referred to the anesthetic. In the search for gunshot wounds, typhoid or tuberculous perforations, the patient may be more or less eviscerated, and if the intestine is roughly handled in the effort to return it, expiration may become so forceful that it is almost explosive in character. This is usually met by the surgeon with still more roughness, and a vicious circle is thus produced. If all manipulations are suspended for a time, the circle will be broken; and if the bowels are now gently handled, there will be no trouble in replacing them. Operations upon the rectum, bladder and perineum produce a reflex inspiratory change of a gasping character. This reflex must not be confounded with the "crowing" sound on inspiration, which is due to a too concentrated vapor. The anesthetization of infants, particularly infants but a few days or weeks old, for intra-abdominal operations, is frequently a difficult task. The successful performance, for example, of such operations as gastro-enterostomy or pyloroplasty may depend to a considerable degree upon the anesthetist.

Temperature of Operating Room, Clothing, Maintenance of Body Heat.—Whenever practicable, it is advisable that the anesthetizing and operating room should be from 65 to 70°F. Temperatures above this are exhausting to the patient as well as to the operator, and are less advantageous than a moderate temperature with the patient well protected. The room should be ventilated but free from draughts. Patients who are about to inhale an anesthetic, whatever that anesthetic may be, should invariably be loosely but warmly attired and only the field of operation be exposed. The operating table should be covered by pads several inches in thickness. Pads can be made of cotton or horsehair, covered with rubber cloth, which prevents fluids penetrating them. A fresh white cotton cover may be used for each patient. Various sizes of so-called "ether blankets" may be made of woolen blankets which, through repeated washings, have shrunk until they are too small to be used on the hospital beds. They should be covered by heavy white muslin and quilted. The muslin covering is a distinct advantage, as it prevents the fuzz from flying about the operating room, and it also simplifies laundering, as it is much easier to remove stains from cotton than wool. Infants and feeble children require special care to preserve body heat. The plan of covering cutaneous areas with wet towels, allowing the patient to lie on a wet pad or table, is open to considerable objection, particularly in cold weather. Of much greater importance than warming ether vapor is the conservation of body heat during anesthesia. Vierdort (Daten und Tabelen for Mediziner) gives 11 calories per hour as the normal elimination of heat by the lungs and 90 calories by the skin. When these figures are contrasted, the necessity of preventing the the loss of heat by the skin through radiation, evaporation or conduction is apparent. The loss of heat is probably due rather to dilatation of the cutaneous vessels than to a disturbance of the heat regulating center or lessened heat production from diminished muscular movements, because the loss of heat can be prevented by covering, or even raised above normal if the patient is surrounded by hot bottles.

Difficulties during Anesthesia.—By the careful observation of symptoms, that is, watching for the slightest deviation from what may be called the normal course, and by correcting or relieving symptoms which are in themselves but trifling, it is often possible to avert respiratory arrest on the one hand or circulatory failure on the other. Crying children are liable to intake large quantities of the anesthetic; and in the administration of chloroform great care must be exercised to allow an abundance of air, or respiratory paralysis may ensue; or in the administration of nitrous oxid it is very easy to induce an undesirable degree of asphyxia. Coughing during the induction period indicates a too-concentrated vapor. Retching and vomiting during the induction period is rare if the patient has been properly prepared, and when it occurs later in the narcosis, it always means a light anesthesia. A tremor which usually affects the lower limbs, but which may be general, occasionally occurs under chloroform, but is more common under ether. As a rule, it may be controlled by changing the position of the limbs or increasing the depth of narcosis.

Many anesthetists have appliances and remedies at hand for use in case of respiratory or circulatory depression. It is far better and much more satisfactory to prevent complications than to combat them after their development. The first step for the relief of respiratory embarrassment is to establish a clear air-way. A mouth-gag should be inserted, and the finger swept around the mouth and back in the pharynx to remove any foreign substance. Place a piece of gauze over the thumb and fore finger, grasp the tongue and draw it forward out of the mouth, holding it in this position. Make regular pressure on the lower part of the sternum with the hand at intervals of a few seconds, thereby causing the elastic recoil to refill the chest with air (Howard method).

Intrapharyngeal or Intratracheal Insufflation.—This technic is identical with these methods of anesthesia except that air or oxygen is forced into the lungs instead of ether vapor, and is administered intermittently instead of constantly. In the intratracheal method, care must be taken not to over-distend the lungs, or a rupture of the air vesicles will result. The pressure should not exceed 30 mm. An ordinary foot bellows or an electric vaporizer may be used to deliver air or oxygen through the tube to the lungs. Intrapharyngeal insufflation is more easily and quickly carried out, because, in the hands of the inexperienced, valuable time may be lost in introducing the catheter into the trachea; but on the other hand, it is not quite so satisfactory because of the difficulty of preventing the escape of the air or oxygen through the mouth or nose, or its entry into the stomach. The lips may be held or fastened together by adhesive plaster; the nasal tubes combined with pressure will prevent the escape of air in that direction. A heavy weight tied over the stomach or deep pressure will keep the air from entering that organ, and has the further advantage of forcing the blood out of the splanchnic area into the general circulation, thus sending more blood to the respiratory and circulatory centers. In very young infants, mouth-to-mouth breathing has been suggested. In threatened respiratory arrest, rythmic compression of the chest wall, each compression being followed by releasing the compression, will force air out of the chest and draw air in by the elastic recoil, which may be sufficient to reëstablish respiration. This method is especially valuable in young children, whose thoracic parietes possess, much resiliency, and usually answers as well as any method of resuscitation in the milder forms of respiratory depression.*

Sylvester Method of Artificial Respiration.—The patient lying flat on his back, with the head lowered and extended backwards, the mouth is held open with a mouth-gag and the tongue held out to insure a free air-way. Standing above the head, the arms are grasped above the elbows and by a forward movement are made to compress the chest walls, causing a strong expiration. They are then drawn outwards and upwards till the hands meet above the head, causing deep inspiration. These movements are repeated regularly about 15 times a minute, or at the rate of normal respiration, until natural automatic breathing is established. Care must be taken not to press too firmly on the chest wall, as there is danger of fracturing the ribs.

The Care of the Patient Following Narcosis.—The rapidity of recovery following narcosis will depend upon the anesthetic employed, the length of the administration and the freedom with which lung ventilation takes place at the conclusion of the administration. With nitrous oxid-oxygen and ethyl chlorid consciousness returns in a few minutes regardless of the length of the anesthesia. Chloroform is slowly eliminated and unless respiration is vigorous recovery may be protracted. When any respiratory embarrassment is present the administration of opiates will prolong the recovery period and tend to enhance the difficulty.

On account of lowered vitality all wet clothing should be removed and the patient well covered with warm blankets to prevent the loss of body heat, on the return journey to his bed. The bed should be warmed with hot bottles and the patient kept warm by covering, and the room well ventilated during the return to consciousness. Sleep should be encouraged by keeping the room quiet and free from anxious friends.

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*It is a mistake, even during such an exciting and serious moment, to place a forceps on the tongue, because of the after-suffering such a mutilating practice inflicts.

Each patient is a law unto himself regarding the taking of nourishment following a general anesthetic. The administration of liquids as soon as possible is especially desirable if shock in any degree is present. They may be given by rectum as soon as the patient is returned to bed or if shock is profound either intravenously or by transfusion. If acidosis is present bicarbonate of soda, 15 to 30 gr. doses, sweetened water, glucose, strained oat-meal gruel should be given as early as possible in order to combat the acid condition (see "Acidosis").

No hard and fast lines can be drawn as to the time food and drink may be allowed after anesthesia. The nature of the operation and the age of the child play an important part as well as the anesthetic administered. As a rule patients may be allowed nourishment by mouth directly following gas anesthesia. If there is no vomiting within a few hours after narcosis the patients may be allowed strained gruels, fruitades, juice of grape fruit or oranges with sugar, hot or cold malted or plain milk. "Soft" foods as oat meal, custards, creamed toast, soft boiled eggs may usually be taken by children within seven or eight hours after anesthesia.

Unless there is a large amount of intestinal distention and gas, bowel movement is not necessary for a couple of days. Colon gas may be removed by the rectal tube. A small enema of equal parts of water and glycerin usually produces an evacuation.

Until the blood pressure has returned to normal or what is satisfactory for that individual, care should be exercised in allowing the patient to sit up or walk after severe operations because of the danger of heart dilatation. During the placing of chest dressings the patient should not be set up or the head and shoulders raised above the body level because of the danger of cerebral anemia and sudden death, especially if chloroform has been administered.

CHAPTER CLXI

LOCAL AND SPINAL ANESTHESIA IN CHILDREN

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LOCAL ANESTHESIA

The element of safety, which must always be the deciding factor in the choice of anesthetics and the growing field of usefulness of local anesthesia entitles this method to a careful consideration. With the development of novocain and other synthetic products which are practically non-toxic in amounts greatly in excess of that necessary to produce adequate analgesia, the range of local anesthesia has rapidly broadened until now it is used in almost every field of major surgery. The work of Schleich with cocain, Henrich Braun, Crile, Matas, Allen and Harris has done much to put this method upon a scientific basis founded upon extensive clinical and laboratory research. The reduction of the hazard incident to the administration of a general narcosis has been the object of these investigators. It is probably true that certain types of cases such as hysterical persons and young children may at times require general anesthesia but the number of these is steadily diminishing with improved methods of technique.

The ancients practiced anesthesia, as recorded by Homer and Virgil, in the form of soothing draughts, probably the juice of poppy and Indian hemp. Pressure upon arterial trunks producing ischemia was in vogue amongst the ancient Egyptians and later the analgesic effect of nerve compression was discovered and used extensively. Strong wine was used in conjunction with these methods and even now whiskey, because of its safety, is the favorite anesthetic with some operators in the performance of harelip and cleft-palate operations upon infants.

While certain of the substances employed as anesthetic drugs by the ancients had some definite physiological effects, by far the greater number only allayed pain through their psychic action, if at all. Thus gold and silver instruments were believed to be less painful than steel.

Local anesthesia may be produced by physical agents or by drugs. Pressure upon a large artery produces an ischemia of the part supplied, which if carried to a certain point causes analgesia of varying degrees. Likewise pressure upon nerve trunks may cause a localized anesthesia the extent and duration of which is dependent upon the degree of pressure. This is a matter of common observation in crutch palsies and nerve compression incident to exuberant callus formation in the healing of fractures and in the more homely expression of "the going to sleep" of a foot after prolonged crossing of the knees. However, as a routine measure in the production of local anesthesia, it is not to be considered safe because the degree of nerve compression necessary to secure an adequate analgesia is quite likely to cause a traumatic neuritis. The careless application of the Esmarch bandage has often been responsible for nerve trauma and venous thrombosis.

The use of cold in the production of local anesthesia dates back to antiquity. Allen states in his work on local anesthesia that Napoleon's chief surgeon reported that at the Battle of Eylau with a temperature of −19 degrees peripheral wounds caused little suffering and that amputations were painless when the limbs were first freely exposed to the air. Cold has been used extensively by the medical profession, first in the form of ice applied to the part, and later in the form of volatile sprays, of which ethyl chlorid is the best known, although many other substances, such as sulphuric ether, chloroform, and carbon dioxide snow, are also in use. Freezing first causes a vaso-constriction followed by dilatation. Because of the danger of necrosis, cold is not suitable for use in major operations or prolonged anesthesia.

Water.—This was first employed by Potain in 1869. It is used especially for neuralgia in the form of acupuncture. When injected too rapidly it produces a burning sensation and may cause necrosis, because the cells absorb large amounts of water and give up their salts, thereby changing their protoplasm. Physical agents have thus far proven inferior to drugs. Amongst the more common agents used for the production of local anesthesia may be mentioned:

Carbolic Acid.—This has a local anesthetic and escharotic action. When injected into the tissues even in weak solution it is likley to produce gangrene. It should never be used as an antiseptic dressing upon a raw surface. At one time it was used in combination with oil, but was not satisfactory. It is now used in a very limited way by physicians in the treatment of hemorrhoids and inoperable malignant growths and is almost a household remedy in connection with glycerine in the treatment of ear-ache.

Chloroform.—This is not a satisfactory agent in the production of local anesthesia because of its slight analgesic effect and because when injected subcutaneously it is very irritating and only slightly diffusable.

Alcohol has recently received a great deal of attention in the production of a more or less permanent anesthesia in the treatment of tic douloureux by paraneural or intraneural injection of the branches of the fifth nerve in 20 to 50 per cent. solutions. It must be remembered in the employment of alcohol, either alone or in combination with other substances that a localized destruction of both sensory and motor filaments takes place when injected into a mixed nerve, giving rise to a motor paralysis which may persist for from 6 to 18 months. In the use of alcoholic solutions it is important to remember that unlike novocain and cocain in aqueous solution, alcohol has little tendency to become diffused. Therefore, it is unsuited for infiltration work.

In 20 to 50 per cent., strength, it is very irritating to the tissues when injected subcutaneously.

Morphine.—Solution of morphine in 4 per cent. strength produces slight analgesia, but the constitutional effect completely over-shadows its local action rendering it unsuitable as a local agent.

Bromides and chloral produce but little local effect, being somnifacients rather than analgesics.

Antipyrin has an analgesic and hemostatic effect, but it is not to be compared to novocain.

Cocain was first isolated as an alkaloid by Gardeka in 1855 and popularized by Koller in 1884. It had long been known to the natives of certain tropical and semi-tropical countries in Central and South America. Its influence, however, as known by these semi-civilized people at an early date differed considerably from the physiologic action of the drug as it is known today. The chewing of cocoa leaves gave to the individual great powers of physical endurance and indifference to pain and fatigue. The leaves were therefore chewed by those in pain and by those undergoing severe physical tests. When the leaves were exported it was found by those who used them for similar purposes that like results were not obtained. This was probably due to the changes incident to drying and transportation (Allen). When applied topically there is rapid absorption of the drug by the skin and mucosa. It first stimulates and then paralyzes the protoplasm. It has a vaso-constrictor action, raising the blood pressure, and producing an ischemia by affecting the motor and sensory nerves. The higher centers of the central nervous system are first stimulated and then depressed. It stimulates respiration. Large doses produce dyspnea, increasing to tetanic convulsions of the respiratory muscles followed by paralysis. It causes marked rise in temperature, 80°F. in fatal poisoning. Cocain decreases excretion of urea and may cause anuria and uremia.

The local analgesic action of cocain is the result of local paralysis of all the tissues (motor and sensory nerves, special sense nerves and muscle fibers). White blood corpuscles lose their ameboid movement under the influence of cocain. Its constitutional action is produced by paralysis of the higher nerve centers.

The soluble salts of cocain are rapidly absorbed even when used topically. Twelve drops of a 4 per cent. solution given hypodermatically caused the death of an 11 year old girl in one minute (Knabi). Twenty drops of a 5 per cent. solution applied to gums proved fatal (Garland).

Individual idiosyncrasy, *e.g.*, poisoning from a small dose, is possibly more to be feared in the use of cocain than in any other drug and this fact did much to delay the development of local anesthesia. Its toxicity varies directly with the amount and concentration of the solution and the rapidity of absorption. Three-fourths of 1 gr. is a safe average dose for an adult. Susceptibility is increased by one poisoning.

General analgesia occurs as the final stage in all severe intoxications.

Combinations of other drugs with cocain, as antipyrin, carbolic acid, resorcin, to combat vaso-constriction have been used.

Koller in 1884 published a work on the local effects of cocain in ophthalmic surgery. The use of this agent was taken up largely by ophthalmologists and laryngologists and since that date has been employed extensively by them. However, it has not been altogether satisfactory since certain individuals show an idiosyncrasy to the drug and in many cases fatalities ensued, as a result of which its use for a long time was confined to the so-called surface anesthesias by which is meant the application of the drug by rubbing or dropping the solution upon the mucous or abraided cutaneous surface.

Symptoms of mild cocain intoxication are loquacity, laughing, singing, nausea, vertigo, faintness, thoracic oppression, rapid pulse, rapid respiration, twitching of muscles threatening onset of convulsions, later maniacal delirium. The pupils are usually dilated.

Ether by inhalation is the best stimulant for cocain poisoning given to the point of mild surgical narcosis by the drop method. The old method of the administration of ether would tend to increase asphyxia. Morphin is recommended as an antidote, but is inferior to the inhalation of ether for cocain poisoning. Intravenous injection of salt solution helps. The onset of toxic symptoms may be delayed for two or more hours, rendering it an uncertain agent to be used upon ambulatory patients.

Adrenalin in combination with cocain intensifies and prolongs its anesthetic action and affords a nearly bloodless operative field. A constrictor may often be dispensed with except in amputations, but when used should always be applied proximal to the point of injection, thereby intensifying the local effect by preventing rapid absorption. Anemic tissues being less sensitive than hyperemic, adrenalin intensifies the local action of the anesthetizing drug. There may be secondary hemorrhage after the use of adrenalin, hence obliteration of any dead spaces to prevent hematomata is necessary.

Synthetic preparations of adrenalin are not yet perfected.

Novocain hydrochlorid is a synthetic preparation with a low toxicity, non-irritating and non-habit forming. It is not suitable for topical application. It is unable to penetrate and anesthetize tissues deeply on topical application, but has wonderful power of diffusion when injected subcutaneously. The medical profession is indebted to this drug for the great impetus given to research in the field of local anesthesia. It is non-toxic to the extent that it is practically always safe to use it in the strength of 0.5 to 2 per cent. in excess of amounts necessary to produce complete local anesthesia, when used by the methods of nerve block and infiltration. The operator must ever bear in mind that the rapidity of absorption of any therapeutic agent is the variable factor upon which the symptoms of poisoning depend. Therefore, one may use large amounts of novocain, without danger to the patient, in those situations from which absorption is slow and where the amount used is spread over a considerable period of time. Novocain may be boiled for one to two minutes without losing its physiological properties.

Chloretone is an anesthetic, antiseptic, and hypnotic agent. It is locally irritating to denuded areas, producing anesthesia in a short time. It is best used as an adjuvant to novocain to prolong analgesia. Chloretone must be added after boiling and cooling the novocain solution because it volatilizes before the boiling point is reached.

Quinine and urea was discovered by Dr. Henry Thibault* of Scott, Kansas, in 1907 and is used in 0.25 to 1 per cent. in sterile water or salt solution. There is usually a burning sensation following the injection of quinine and urea hydrochlorid.

The after effects are prolonged as compared to other agents. Allen cites hemorrhoid cases in which the patients complained of no post-operative pain after its use. As a topical application in 15 to 20 per cent. solution it is not to be compared to cocain, although it is practically non-toxic when applied to a mucous surface.

Hertzler, Brewster and Rogers† proved that the induration following quinine and urea injection was not due to cellular infiltration but to fibrin deposit. This occurs always after injection of solutions above 0.25 per cent. strength.

Allen advises the use of 0.25 per cent. solution in clean operative fields, but in those situations where primary union cannot be expected and where the prospect of hemorrhage is a factor of importance, the stronger solutions up to 3 per cent. are preferred because of their marked hemostatic action, resulting from the fibrin deposit.

The duration of the analgesia when used in strong solutions, e.g., up to 3 per cent., is from 7 to 10 days (Allen).

It has been used by Matas in the treatment of trigeminal neuralgia.

Allen cites a case of strangulated hernia operated under quinine and urea, 0.25 per cent. solution, in which the sensitive peritoneum was anesthetized and adhesions broken up after pouring 2 drams of the solution into the peritoneal cavity.

One hundred grains of the quinine and urea have been injected in the course of six hours without toxic results.

Its local action is less rapid than cocain, novocain and B-eucain, yet the analgesia is more prolonged.

It is less diffusible.

Quinine acts as a vasodilator and favors capillary oozing. Later the fibrinous exudate tends to cause coagulation.

The fibrinous exudate is dependent upon the concentration of the solution.

Cases of tetanus have been reported following the use of quinine and urea hydrochlorid. Semple recommends injection of 10 to 15 c.c. of anti-tetanic serum when quinine and urea are to be injected hypodermically or intramuscularly.

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* Jour. Ark. Med. Soc. (Sept. 15, 1907).

† Jour. A. M. A. (Oct. 23, 1909).

Magnesium Salts.—The anesthetic properties of these salts were discovered by Dr. S. J. Meltzer of New York.

Magnesium salts applied to sensory trunks inhibit conductivity. Intra-cerebral injections produce general inhibition. Subcutaneous injections produce deep narcosis and complete muscular relaxation. Intravenous injection produces the same effect and inhibits intestinal peristalsis. Subcutaneous and intravenous injections have produced complete muscular relaxation in tetanus lasting 24 hours. When applied locally to an open wound no effect is produced.

Guthrie and Ryan believed magnesium salts produce general muscular relaxation so that animals cannot respond to stimuli, and when general anesthesia was produced it was due to a paralysis of the respiratory muscles, causing asphyxiation. This theory was later disproved by Meltzer by intraspinal injection of magnesium sulphate in human subjects, who remained conscious without disturbance of respiration, although completely anesthetic below the point of injection.

Technic of Local Anesthesia.—The operator must constantly bear in mind during the performance of an operation under local anesthesia that while the employment of cutting instruments causes no painful sensation when the infiltration and nerve block have been properly carried out, rough manipulations and gauze dissection are painful because of the traction upon nerve trunks. This fact is greatly to the advantage of the patient in that it necessarily minimizes operative trauma. Tissue repair is therefore more rapid and the habit of tying ligatures to the point of tissue strangulation is overcome because of the pain incident to such practice. Delicate handling of tissues and careful sharp dissection constitute an important element in the technic of local anesthesia. The duration of the operation is unimportant as compared to the danger of a prolonged general narcosis.

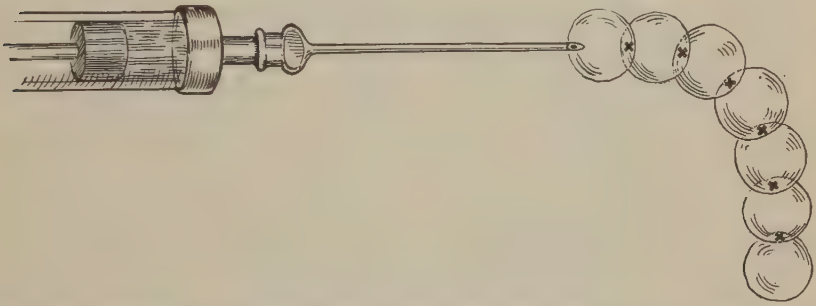

FIG. 82.—Method of injecting skin. The first introduction of the needle only is painful as each succeeding thrust is into a desensitized area.

In the technic of infiltration the point of a fine hypodermic needle is introduced into the skin producing a wheal about the size of a split pea. The needle is always reintroduced through the last wheal and these are so situated that they overlap each other forming a slight

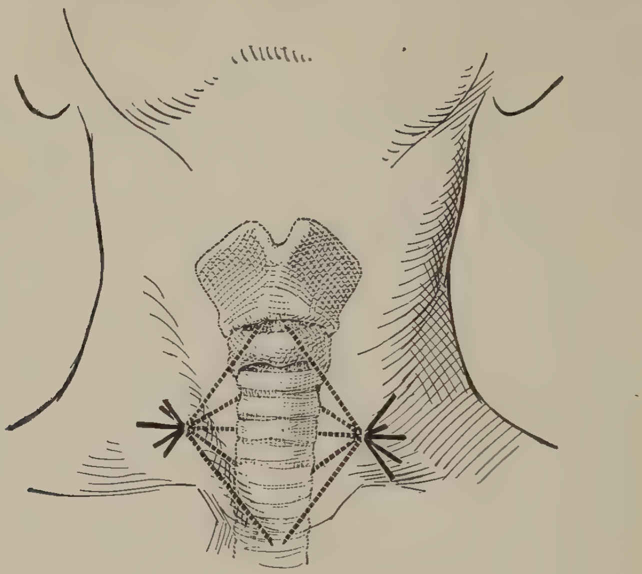

FIG. 83.—Points of injection for local anesthesia for tracheotomy.

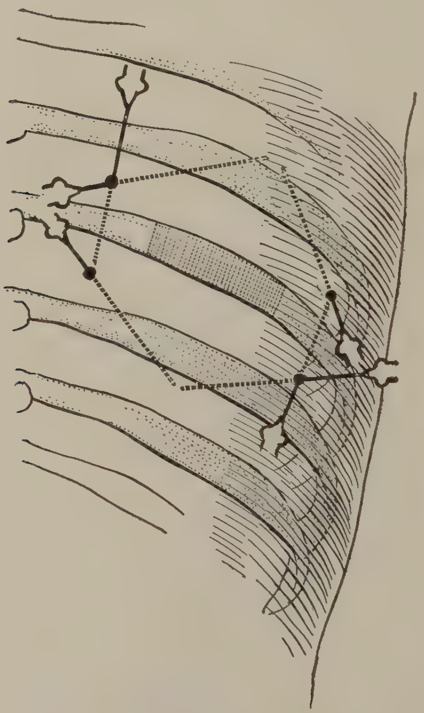

FIG. 84.—Blocking intercostal nerves.

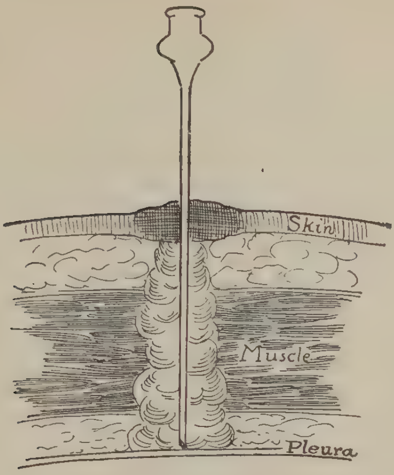

FIG. 85.—Method of anesthetizing the pleura.

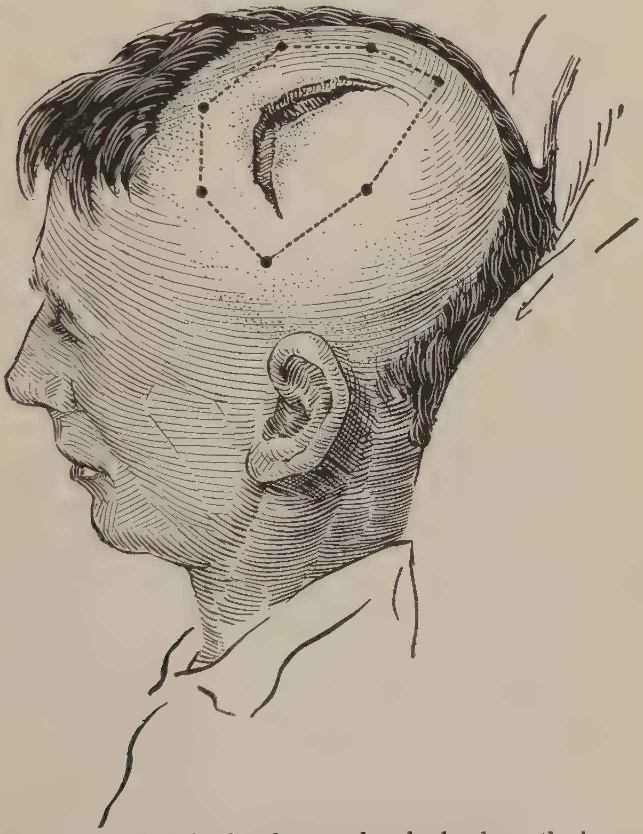

FIG. 86.—Repair of scalp wound under local anesthesia.

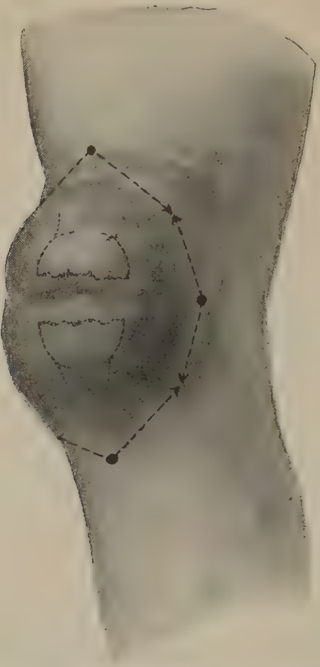

Fig. 87.—Points of injection for local anesthesia for repair of fractured patella.

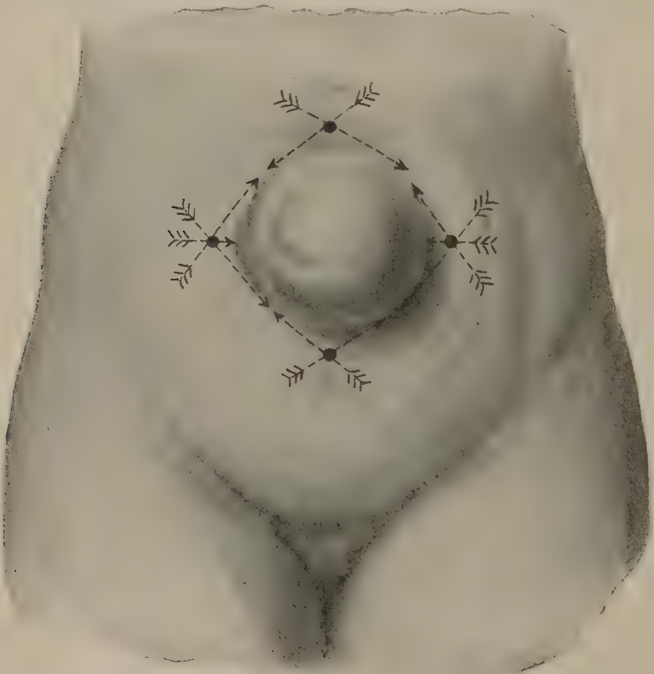

Fig. 88.—Points of injection for local anesthesia for umbilical hernia.

ridge. This is paler than the surrounding skin because of the tension. The intradermal or infiltration method is the injection into the skin, not beneath it, of analgesic solutions producing a series of wheals which form a continuous line. This paralyzes the sensory nerve endings in the papillary layer of the skin.

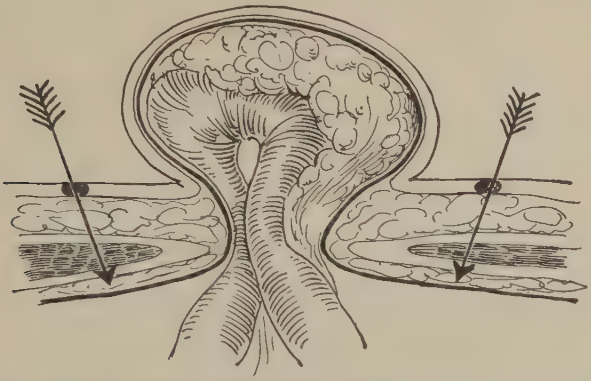

Fig. 89.—Strangulated hernia. Method of producing local anesthesia for relief of strangulation.

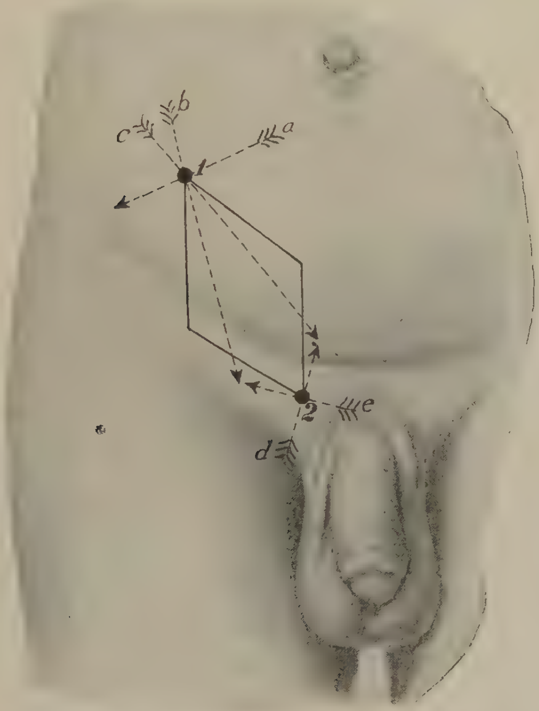

Fig. 90.—Points of injection for nerve block and infiltration for inguinal hernia.

The tissues are sensitive to very dilute solutions of drugs, while simple edematization of the skin with isotonic sodium chlorid solution produces analgesia.

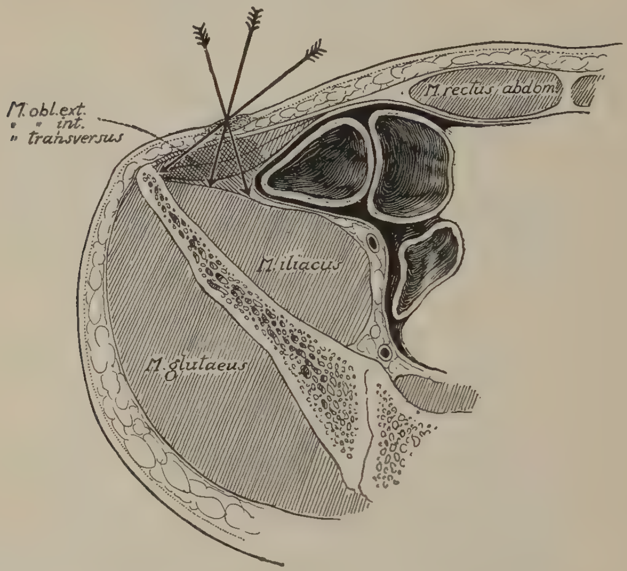

Fig. 91.—Deep infiltration of tissues for local anesthesia in inguinal herniotomy.

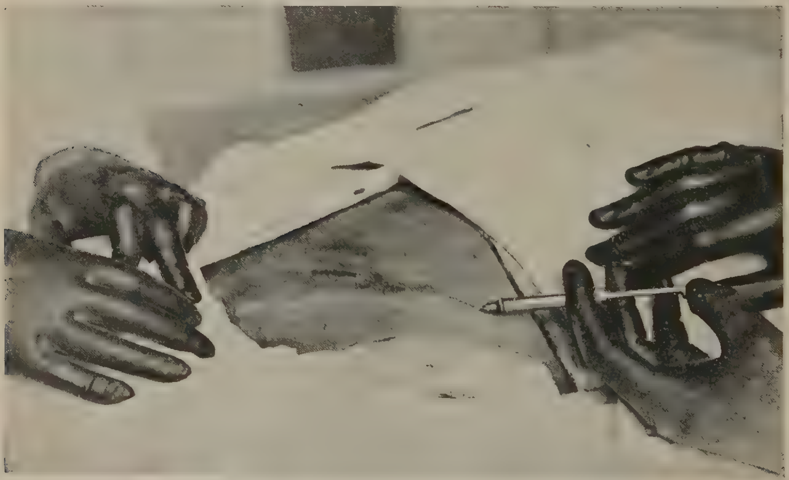

Fig. 92.—Infiltration of skin for inguinal hernia.

The action of any agent is prolonged by the use of a constrictor, either in the form of adrenalin added to the analgesic solution or by the application of the Esmarch bandage.

The infiltration of nerve trunks or posterior spinal roots by intraneural or paraneural injection causes sensory paralysis distally to the point of injection. This method is known as nerve block and is equivalent to section when properly carried out.

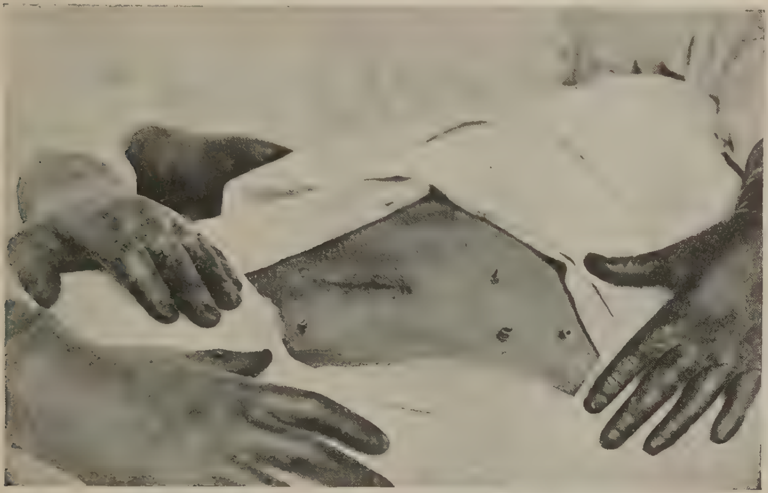

FIG. 93.—Nerve block for inguinal herniotomy.

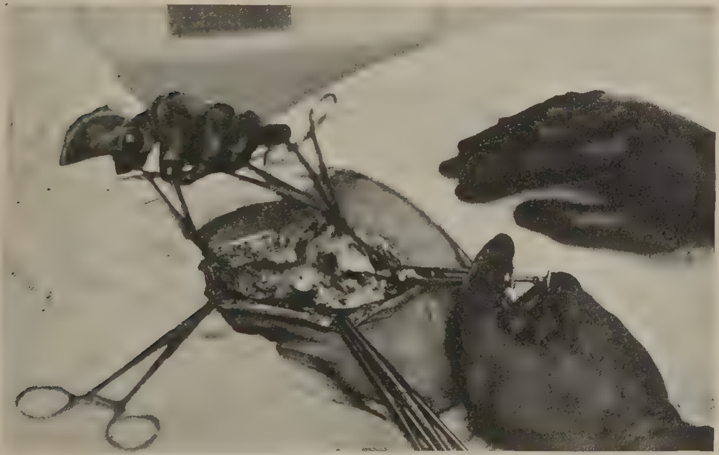

FIG. 94.—Infiltration of sac.

The analgesia thus produced is usually sufficient for surgical work, although tactile sensation may be preserved. The preliminary injection of morphin and scopolamin is usually advisable to produce tranquility of mind. This is greatly helped by the assistance of a good nurse to act as a so-called "moral anesthetist," quieting the patient's fears by diverting his attention and reassuring him. Women are much preferable to men for this work.

Menstrum for anesthetic agents:

Hypertonic.
Isotonic.

Hypotonic salt solutions or water may be used as menstrum for anesthetic agents.

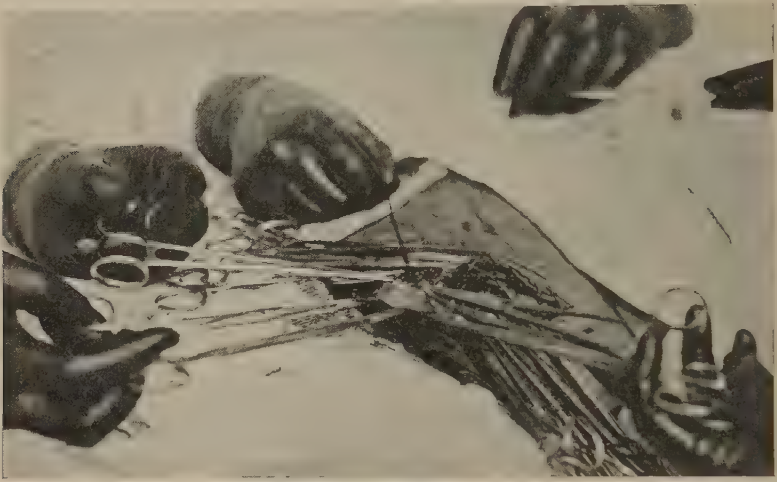

Fig. 95.—Amputation of sac.

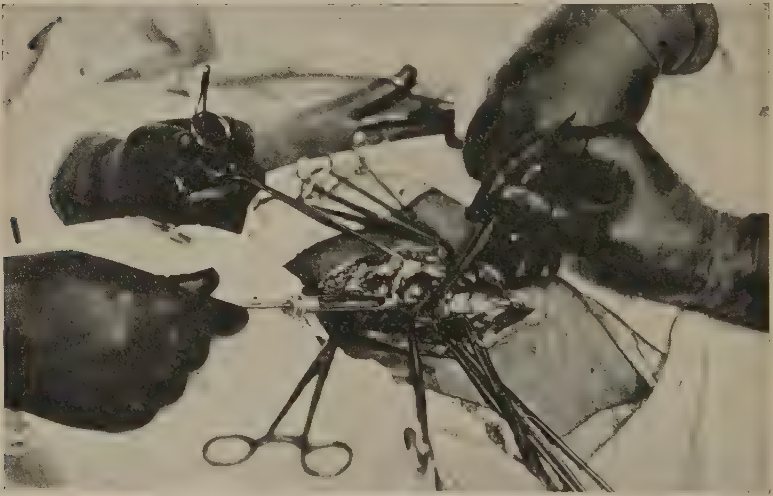

Fig. 96.—Repair of hernia.

Morphin (gr. 1/6 to 1/4) and scopolamin hydrobromid (gr. 1/150 to 1/100) may be given 30 to 45 minutes preliminary to local anesthesia. Their effect lasts six to eight hours and makes unnecessary post-operative hypodermics of morphin in most cases. In children the dose should be reduced according to the age and condition of the child.

Novocain may be used as follows:

Novocain	0.25	1.0	2.0
Aq. Dest.	100.00	100.0	100.0

Novocain may be boiled for one minute without deterioration. The addition of adrenalin is contra-indicated in patients with high blood pressure and hyperthyroidism, but may be used to advantage in most cases because of its property of localizing the action of novocain. Solutions should be freshly made.

SPINAL ANESTHESIA*

Stovain in solution is heavier than spinal fluid. The field to be anesthetized includes the lower rectum, anus, perineum, genito-urinary tract (except kidneys and ureters), all varieties of hernia except those occurring above the umbilicus, appendectomy and all operations on the lower extremity.

The dose is small and confined to the lower part of the subarachnoid space, thus rendering collapse and respiratory paralysis the only really dangerous complications; other complications are practically impossible. The percentage of failures is almost nil.

The duration of anesthesia should be sufficiently long to make muscular relaxation complete. The hemorrhage is lessened because of vasomotor paralysis and lowered blood pressure, and anociation is perfect. The anesthesia is complete in 2½ minutes.

The Trendelenburg position is dangerous as it permits upward diffusion of the drug, causing respiratory paralysis. Vomiting frequently occurs.

Spinal anesthesia is not sufficiently satisfactory for operations on the upper abdomen and thorax to be recommended for general use, and is too dangerous to be used in operations on the neck and head.

Contra-indications.—(1) In cases of hypotension from shock, hemorrhage, etc. (Normal salt containing adrenalin given intravenously during the anesthetic combats lowered blood pressure.)

2. Old and asthenic patients.

* Yount, C. C., S. G. O., xxv, No. 1, p. 40.

CHAPTER CLXII

SOME MEDICOLEGAL ASPECTS OF ANESTHESIA

By F. H. McMechan, M.D.

Avon Lake, Ohio

While the anesthetist is bound by those rules which govern the professional conduct of all registered and licensed practitioners, in many respects, his or her position is ill defined and subject to modifying circumstances. This is due to the fact that only during the last few decades has the anesthetist been acquiring some independence, and consequently only a limited number of legal decisions are available for his guidance.

In the ordinary routine of his work the first legal obstacle that confronts the anesthetist, as well as the surgeon, is the question of consent.

Consent.—No person can be anesthetized legally without consent unless the anesthetist opens himself to a charge of assault. In the case of children and the insane, consent must be secured from parents, guardians, or those legally authorized to give it. In England,* it is held that the power of a parent to withhold consent, even to a necessary operation, is absolute. In American courts of recent years, judges, at the instigation of health authorities, juvenile court officers, or relatives, have removed children from the guardianship of one relative to that of another to assure proper medical attention. It seems probable that a similar jurisdiction would be exercised to enable qualified official physicians to perform operative procedures under anesthesia, especially in cases of emergency, without direct parental consent or in spite of prejudiced objections to operation or anesthesia.

It is also obvious that many young people, particularly among the working classes, although legally *not of age* are practically independent of their parents. The Canadian courts† furnish a case turning on this point. The patient had agreed to an operation, to which his parents had not consented and the judge's decision was against their protest, on the intrinsic merits of the individual case, rather than upon any fixed principle or newer interpretation of the law.

Actions have been brought for alleged anesthetization without consent, especially when the patient and anesthetist have been alone together and the anesthetist has also assumed the rôle of operator. The majority of these cases have failed on the grounds that anesthetization *by force* was impossible and that there was collateral evidence of consent; but in each instance anesthetists have been put to the inconvenience of framing a legal defense.

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* Lancet (May 6, 1911), p. 218.

† Mortimer, J. D., Anesthesia and Analgesia (1914), p. 256.

It must also be remembered that in the employment of untried anesthetic agents or in initiating newer methods of administration, a grave responsibility rests with the anesthetist, unless the patient is fully advised of the experimental character and possible untoward results of the procedure and his consent to the trial has been previously obtained.

Two very important questions now arise. Who is legally qualified to administer anesthetics and what legal regulations regarding the administration of anesthetics have been promulgated?

The limiting of the administration of anesthetics to legally qualified practitioners has been presumed in the context of the various state medical practice and license laws, without having been definitely expressed. The nurse-anesthetist abuse, endorsed and perpetuated by certain surgical clinics, has insidiously crept into the ranks of the profession. There is no Nurses' Registration Bill extant that expressly conveys the legal qualification to administer anesthetics.

An opinion recently (1918) handed down by the attorney general of West Virginia probably expresses better than any other the fundamental medicolegal aspects of non-medical persons administering anesthetics. The vital portion of the opinion is as follows:

Under the law the right to administer drugs used in surgical anesthesia by a person not a licensed physician would not depend upon either the question of preparation by study or otherwise, or compensation or fees charged for service, but upon the question as to whether or not the administration of such drugs would constitute the *practice of medicine and surgery* within the meaning of the statutory definition. Is the administration of the anesthetic preparatory to a surgical operation an integral part of the operation itself? I think it is.

There are certain things preparatory to a surgical operation necessary to be done that can be trusted to nurses and attendants, which are really not a part of the operation itself, and require no great amount of skill to perform. *However an anesthetic is a substance the unskilful handling of which is dangerous to human life. The person undergoing the operation places himself absolutely under the control of the person administering the anesthetic. This is the first dangerous step in the operation; the first one requiring peculiar skill and knowledge.* The operating surgeon concentrates his attention on the cutting part of the operation and cannot well exercise careful supervision over the person administering the anesthetic. The anesthetic is such a subtle and dangerous agent that the most careful supervision on the part of the operating physician does not remove the danger of it in the hands of the unskilful person.

If it is held that the administration of anesthetics does not constitute the practice of medicine and surgery, then the fitness of a person to administer them is determined in each case by the operating surgeon. He would constitute the examining tribunal and might choose either a skilled or unskilled person to perform a recognized dangerous part of the operation. I do not believe the legislature ever intended that any person not a licensed physician should be permitted to administer drugs used in surgical anesthesia, even though such a person may act under the direction and in the presence of a licensed physician and surgeon.*

In the case of *Nations Ludington, Wells and Van Shaick Lumber Co.*, the patient, an employee, died from the effects of chloroform, administered by a nurse, before the operation was begun on his crushed hand. The Supreme Court of the State of Louisiana held that employment of a non-medical anesthetist, with no emergency existing and physicians available for the purpose, constituted negligence and increased the damages awarded by the trial court to $10,000. The Supreme Court in this case was emphatic in its declaration that in the case adjudicated, one contemplating minor surgery only, a physician should have been called and employed to administer the anesthetic, instead of the chloroform being administered by a nurse, in the presence and under the general direction of the operating surgeon.

In August, 1909, the chief of the Board of Health, Vienna, issued to all hospitals and out-patient departments of the late Austro-Hungarian empire, the following regulations regarding the administration of anesthetics:

1. To have each and every patient especially examined before being put under the influence of an anesthetic.
2. To limit the use of inhalation anesthesia to the cases in which this method of narcosis was absolutely necessary. In all other instances local or regional analgesia was to be considered the method of choice.
3. Under no conditions would the same physician be allowed to anesthetize and operate upon a patient.
4. Legally only qualified medical men would be privileged to administer anesthetics.
5. Students would be permitted to administer anesthetics only after instruction and then only under proper supervision.
6. Finally, the chemical purity and non-deterioration of the anesthetic agents would have to be determined before use.†

Certainly this is a set of regulations worthy of the highest commendation and the most widespread promulgation on the part of the Health Departments of our various states and cities, particularly in those medical institutions within their immediate control.

The state of New York has incorporated a section regarding anesthetics in its penal code. This section reads as follows:

Section 1752.—A person, other than a duly licensed physician or surgeon engaged in the lawful practice of his profession, who has in his possession any narcotic or anesthetic substance, compound, or preparation, capable of producing stupor or unconsciousness, with intent to administer the same or cause the same to be administered to another, without the latter's consent, unless by direction of a duly licensed physician, is guilty of a felony, punishable by imprisonment in the state prison for not more than 10 years.

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* Am. J. Surg., Anesth. Sup. (October, 1918), p. 133.

† Brit. Med. J. (Aug. 21, 1909), p. 496.

Responsibility.—The occurrences of fatalities or untoward results under anesthesia bring the anesthetist before the bar of coronial inquiry and leave him open to suits for malpractice or prosecutions for manslaughter.

Mortimer suggests that in becoming a *specialist* the anesthetist opens himself to actions for damages on account of injuries sustained during anesthetization; for example: The breaking off of a tooth from forcibly opening the mouth; injuries sustained during struggling; bruising of the tongue; accidents or failures such as loss of an eye from a movement of the head or the inability of the surgeon to complete an operation; or from such after-effects as brachial paralysis, or burns from hot-water bottles. While there is considerable speculation in the foregoing, still the anesthetist, through carelessness, may readily bring a damage suit upon the head of the operating surgeon or the trustees of his hospital.

Damages.—The most prolific source of actions for damages in connection with anesthesia has been the burning of patients by hot-water bottles while still under the influence of the anesthetic. Chief Justice Riddell of the Supreme Court of Ontario, Canada, found this subject of sufficient importance to deal with it at length in *The Nurse* in 1916, shortly after allowing an appeal in the case of *Levere vs. The Smith Falls Hospital*, and entering judgment for the plaintiff in the sum of $900 and costs. In rendering the decision and summing up various cases and decisions as precedents, pro and con, Chief Justice Riddell lays stress on the fact that the inviolability of charitable trust funds was no longer tenable and they could be diverted to the payment of damages. His decision was in consonance with that of the Supreme Court of South Carolina in *Lindler vs. Columbia Hospital*, in which the court held that a strong declaration of liability was necessary to cover the underlying principle involved—absolute immunity from the results of criminal, as well as careless negligence, on the part of employees of a hospital which could secure a charitable foundation. The court held also that as the charitable foundation called for the relief of suffering, it was only consistent with strict justice for such a fund to repair the evil of its own doing (81 S. E. R. 512). In a similar case, *Tucker vs. Mobile Infirmary Association*, the Supreme Court of Alabama held (1) that there was no difference between the case of a patient with an *express* and *implied* contract, and (2) that a charitable hospital is in no higher position than any other corporation in respect to liability for the negligence of its servants, the *charitable trust theory*, although supported by a great weight of authority in the American courts, being untenable. Among similar cases of interest may be mentioned *Hillyer vs. Govenors of St. Bartholomew's Hospital* (Court of Appeal, England), *Ward vs. St. Vincent's Hospital* (Supreme Court of New York), *Chilley vs. Bradford*

(Lancet, Jan. 31, 1914), *Reeves vs. Lutz* (Court of Appeals, Missouri), and *Stewart vs. Manasses, Pa.* (90 Atl. R. 574).

In those cases arising from deaths under anesthesia, which have come to trial in English and American courts on pleas for damages or on prosecutions for manslaughter, the following defense has always proved successful: (1) That the administrator was a qualified medical man, and (2) that both the operation and anesthetic were necessary; that (3) the administration was conducted with the experience and knowledge ordinarily demanded, and that (4) death was unavoidable and not due to carelessness or want of skill.

Compensation.—Reporting to the Interstate Association of Anesthetists at its meeting Sept. 25, 1918, Dr. A. S. McCormick detailed a personal case in which Justice C. W. Dickerson of Akron, O., on Apr. 7, 1916, held the defendant to the payment of an anesthetist's fee and court costs, irrespective of his plea that he had not engaged the anesthetist. Similar and pertinent cases are the following: 64 Com. 432; 40 Iowa 84; 47 Iowa 625; 138 N. Y. 1072; 139 N. Y. 934; 67 Wis. 572. In all these cases it was decided that if an assistant be required the physician in charge may engage him, and the patient, whether consulted or not, is legally responsible for payment of the assistant.

CHAPTER CLXIII

THE PECULIARITIES OF SURGERY IN CHILDHOOD

By Dean Lewis, M.D.

Chicago, Ill.

The subject of pediatrics is divided into different age periods—newborn, infancy and childhood—based upon the various stages the child passes through in its development. Pathologic processes in children do not differ from those in adults, the tissues reacting to a stimulus or toxic substance in much the same way. Certain processes, however, are peculiar to the child. The pathologic processes may be most easily considered under infections, malformations and tumors. These will not be considered in detail in this chapter for the special pathology will be discussed more in detail in the chapters dealing with the diseases of the organs or special systems.

The newborn is susceptible to infections. The phagocytic properties of the leukocyte are not established, and the lymphatic apparatus does not yet react to the infective processes. Bacteria may gain entrance through the umbilicus, through small fissures and through the intestines, which afford a ready means of access for bacteria. The intestinal walls of the newborn seem to be permeable to bacteria which those of older infants, children and adults, and even experimental animals, do not permit to pass. Organisms rarely enter the general circulation by way of the genital and urinary tract in the newborn, although these form a common route of infection later in infancy. Czerny and Moses have found microörganisms in the blood of children in the first weeks of life, who presented clinical evidence of general infection. Organisms thus circulating in the blood may, as in adults, lodge in different tissues where a *locus minoris resistentiæ* is provided and may be the cause of an osteomyelitis in a simple fracture, of muscle and subcutaneous abscesses and infection of the viscera. Organisms which arrange themselves in groups or clumps thus form occluding emboli. Such organisms as the staphylococci and gonococci are more apt to form these secondary abscesses.

Lenhartz's statistics are interesting as indicating the frequency with which different bacteria form metastatic or secondary abscesses.

The following table indicates the frequency:

Bacteria	Number of cases	Without metastases, per cent.	With metastases, per cent.
Streptococci	100	65	35
Staphylococci	22	5	95
Pneumococci	20	75	25
Bacterium coli commune	8	78	22

A general infection due to gonococci also shows a high percentage of secondary or metastatic abscesses. These add to the gravity of the case because of the number of organs which may be involved and the difficulties often encountered in evacuating the pus.

The Umbilical Cord.—Infections of the umbilical cord frequently occur during the first week when it is separating. Some discharge begins, either serous or purulent, in sufficient amount, perhaps, to moisten a dressing and when the cord is lifted the surface of the umbilicus will often resemble an ordinary granulating surface which is discharging. In severe cases a phlebitis may develop, causing a general infection with multiple abscesses, due to the lodgment of bacterial or infected emboli.

In severe types the inflammatory process may extend to the skin surrounding the navel. This may resemble erysipelas or a phlegmonous process, and may occur in the second or third week after the separation of the cord. Gangrene of the cord, which resembles hospital gangrene, is no longer seen. This type of infection was caused probably by a specific microörganism and being extremely rare, is now a pathologic curiosity.

Noma.—Noma is a peculiar inflammatory process ending in gangrene which is rarely seen at present. It occurs almost exclusively in weak, emaciated children from 2 to 12 years of age. These children generally live in the poorer districts of large cities under squalid conditions. A number of infectious diseases have been known to precede the development of this disease. A number of different bacteria and fungi have been found in noma and this can be easily explained when it is remembered how great a variety of bacteria are to be found in the mouth. This process usually begins as an abrasion or an inflamed area near the angle of the mouth, occasionally in the mucous membrane of the palate, lips or gums. A vesicle with cloudy contents or a superficial ulcer usually precedes the development of the gangrene. As the gangrene spreads, the bordering tissue becomes inflamed, indurated and hard. The skin, which exhibits a marked pallor, becomes discolored bluish-black. This dark gangrenous area sloughs out during the first week leaving a large defect in the cheek and often, as the cicatricial tissue develops, seriously interfering with movements of the jaw.

Bone Infections.—Infections of bone offer one of the most important and interesting problems in the pathology of childhood.

The infections are frequent and they occur in childhood because of the conditions encountered in rapidly growing bone. The infection of osteomyelitis may develop in any part of the skeleton during the period of development.

The long bones are most usually the seat of this disease, those of the lower extremity being most frequently attacked. The infection most often occurs in the metaphysis, the spongy end of the shaft lying next to the epiphysis. Osteomyelitis attacks not only the long bones, but may occur in the bones of the hand and foot, in the ilium, scapula, vertebræ, etc., but by all odds the long bones are most frequently involved.

Tuberculous foci occur most frequently in the ends of long bones, in the epiphyses, in the vertebræ and such bones as the metacarpal and metatarsal, while infections due to pyogenic organisms occur most frequently in the metaphyses of long bones. This statement is correct in general, but such recent work as that of Lovett, in which accurate bacteriologic controls of bone infection were secured, seem to indicate that many of the infections occurring in the shaft of the long bones of children, even when surrounded by heavily sclerosed bone such as might be found in pyogenic infections, are really tuberculous.

The arrangement of blood-vessels in young growing bones apparently favors considerably the localization of bacteria. The arteries of the long bones of newborn and small children may be divided into three sets. The most important is naturally the nutrient artery. In its beginning such an artery is frequently tortuous. The nutrient artery of the femur shows such a condition, the branches passing in opposite directions. These arteries communicate with each other by fine anastomoses in the marrow. In the tibia the smaller branch of the nutrient artery runs toward the upper epiphysis, while the larger runs toward the lower. The branches of the nutrient artery continue into the spongy bone of the ends of the diaphysis. The terminal branches run close to the epiphyseal cartilage. If this does not occur a second system of vessels is found which pass toward the epiphyseal cartilage, sending branches toward the diaphysis and the cartilage which may be perforated by them. These arteries, which may be called the metaphyseal, are of great significance because of their relation to the localization of certain bacteria.

The third system of vessels are the epiphyseal. These vessels in general pass in toward the center of ossification, some passing toward the epiphyseal cartilage, some into the epiphysis proper, so that the latter is supplied by both metaphyseal and epiphyseal vessels.

The older the bone the smaller the vessels relatively and the less numerous, but even at the conclusion of growth the three systems just described may be made out. In the metacarpal bones and phalanges, the nutrient artery is large and suddenly breaks up into finer branches.

described may be made out. In the metacarpal and phalanges, the nutrient artery is large and suddenly breaks up into finer branches.

Emboli would lodge in the nutrient artery itself and this probably accounts for the clinical picture of spina ventosa in tuberculosis. In the adult the relation between the diaphyseal and epiphyseal vessels is reversed. The nutrient artery is smaller, while the epiphyseal vessels, penetrating the bone transversely in the region of the epiphysis, are larger in size, being about that of the nutrient artery in bones of children.

Tuberculosis of the bone is caused by infected or bacterial emboli, which lodge most frequently in the epiphysis or metaphysis. Suppurative foci caused by staphylostreptococci and pneumococci may have much the same location, being due to bacterial emboli. Staphylococci are more frequently found in osteomyelitis because they form groups which give rise to an embolic process. The great vascularity of the ends of long bones associated as it is with a distinct slowing of the bone stream probably accounts for their more frequent involvement in acute suppurative osteomyelitis than that of the vertebræ and metacarpal and metatarsal bones.

Different changes may occur depending upon the direction in which the inflammatory process extends. (1) If it extends along the marrow cavity, it may pass rapidly from one epiphysis to the other causing total sequestration of the shaft or a tubular sequestrum. In pyogenic infections of bone, proliferative processes are associated with necrosis and the periosteum, stripped from the shaft, proliferates to form an involucrum. This may be pierced in many places by openings through which pus is discharged. These openings in the involucrum are called the cloacæ. (2) The process may extend directly across or along the epiphyseal cartilage causing epiphyseal separation. (3) The inflammatory process may extend through the epiphyseal cartilage where vessels perforate it. (4) The process may extend through the epiphysis, breaking into the joint. (5) The process may be situated somewhere near the surface and rupture through the periosteum. Depending upon the relation of the point of rupture to the capsular ligament, joint involvement may or may not occur.

Pneumococcic and streptococcic foci in children have this peculiarity, that they may break through below the attachment of the capsule and the clinical picture may be that of an arthritis, the primary bone involvement being determined by *x*-ray examination, if suspicion is aroused, when the lesion does not heal after being incised, because of a sinus leading down to exposed bones of the knee joint when the lower end of the femur is involved.

Tuberculosis most frequently attacks the epiphysis, entering either as infected or bacterial emboli. Bones such as the vertebræ, the metatarsal and metacarpal bones and phalanges are particularly prone to involvement. Tuberculosis causes caries without much proliferation on the part of the surrounding bone or periosteum. The reaction which occasionally occurs may lead to a sclerosis of bone not unlike that occurring about a bone abscess caused by pyogenic microörganisms. Caseation occurs as the bone breaks down.

Because of the frequency with which tuberculosis attacks the epiphysis, the inflammatory changes in the joint overshadow the infection in the bone. Caries sicca and diffuse tuberculous osteomyelitis are observed in adults.

Syphilis of bone occurring in children is not infrequently characterized pathologically by a gummatous osteomyelitis affecting the metacarpal bones and phalanges and resulting in expansion of the bone. A thickening also occurs due to the proliferative changes in the periosteum. The pathology of congenital syphilis of bone will be described later in describing syphilitic osteochondritis.

If a gummatous inflammation of bone develops in early childhood (the disease being either acquired early or being congenital) a deformity may develop in one or both legs. In these changes, described by Fournier as osteitis deformans syphilitica, the tibia becomes lengthened, curved forward and thickened. A prominence develops upon the anterior surface rather low down. The saber-sheath deformity of the tibia is due to the thickening and lengthening resulting from the inflammation. The curving forward of the tibia is probably static and compensatory.

When a gumma develops in bone two processes, one destructive, the other constructive, proceed together. The granulation tissue of the gumma invades or infiltrates the bone causing caries, while the neighboring bone is stimulated to the production of new bone. The bone enlarges and the surface of the diseased bone becomes irregular, roughened and eroded.

Peritonitis.—Peritonitis in children may be due to a variety of causes, being secondary to perforation of the appendix or viscera or to the streptococci or tubercle bacilli. The pathology of peritonitis does not differ from that in the adult with the exception that the omentum may not be so active as it is in the adult in localizing and walling off the infection, the omentum being poorly developed in children. Pneumococcic peritonitis is a form of infection which belongs especially to childhood. This type of peritonitis is not restricted to childhood for it is found fairly often in the adult. It is far more common, however, in children.

The encapsulated or encysted variety of pneumococcic peritonitis is not the most common form, although generally regarded so. In the encysted forms a large amount of pus may collect, leaving when evacuated a large cavity, which is bounded below by the pelvis, posteriorly by the abdominal wall. The intestines are usually carried up by this collection of pus so that the cavity is limited above by coils of intestines. The pus is characteristic of that of empyemas and arthritides due to the pneumococcus. It is thick and creamy in consistency and white or grayish-white in color. Its odor is not foul; thus it is differentiated from the collections of pus associated with appendicitis. Fibrinous flakes or masses within the pus commonly occur.

In diffuse cases the intestinal loops are injected. Between these injected loops, which are often not adherent, large quantities of odorless, greenish pus may be found. In the cul-de-sac of Douglas the pus may contain masses of fibrin and have a creamy consistency. Small, enlarged lymph-nodes may be found in the mesentery. In many of the cases which have come to necropsy no microscopic changes in the mucous membrane of the intestines, such as ulcers or deposits of fibrin, have been found. In some instances examination of the intestinal contents has revealed an organism resembling the pneumococcus. A generalized peritonitis may follow a pneumococcic infection of the lungs, but in the cases in which the disease is primary in the peritoneum, the encysted form is probably more common.

Lymphatic Nodes.—The lymphatic nodes in the child are frequently the seat of inflammatory processes, those in the neck being frequently affected. The affection may be acute or chronic.

Routes of infection leading to acute suppurative changes in the lymph-nodes are many. In the neck such infections may follow abrasions or excoriations of the skin, infections of the external ear, of the mucous membrane of the nose, mouth and pharynx. Inflammation of the lymph-nodes of the extremities, axilla or groin may follow any one of a number of infections of the extremities.

The lymphadenitis in children secondary to the lesions just mentioned is not like that following severe infections in which the nodes become enlarged and matted together by a peri-adenitis and an edema of the surrounding tissue. In children the infections are apt to be mild, the gland breaking down early and often breaking through the capsule to form a localized phlegmon or abscess. The process occurring in such glands does not differ in any way from an ordinary pus infection of lymph-nodes.

Chronic Lymphadenitis.—Enlargement of cervical lymph-nodes may follow an eczema or fissures of the nose and lip and long-continued pathologic changes in the mucous membrane which they drain. Such nodes are movable, they are apt to be indurated and may continue for years without undergoing any definite changes.

In about 90 per cent. of the cases of tuberculosis of lymph-nodes the cervical group is involved. In children tuberculous glands tend to caseate and the disease thus will remain localized to one gland or one group of glands—forming an abscess. Abscesses may occur from time to time in such a group as the glands adjacent to the node originally affected break down.

In some cases the nodes instead of softening may undergo a pure hyperplasia but few tubercles developing. The increase in size frequently is due to changes in the reticulum of the lymph-node. Such glands may resemble, as far as macroscopic appearance is concerned, those of pseudoleukemia.

In some forms of tuberculosis of lymph-nodes caseation with liquefaction does not occur, the glands do not become fused, remaining isolated and a whole chain of nodes varying in size may be found on palpation. Such nodes are fairly firm in consistency, are round and freely movable.

MALFORMATIONS

In order to understand the different malformations it is necessary to have a clear understanding of the different embryologic processes. Many deformities are caused by the failure of clefts to close, by the fusing of adjacent structures, or because certain epithelial concrescences, which appear normally in the developing embryo, fail to disappear.

Face.—In the second or third week of fetal life the first anlage of the face appears as a structure surrounding the so-called primitive mouth cavity. In the earliest stages this cavity is bounded above by the developing head, below by the first branchial arch. The relatively wide opening decreases in size as the head and branchial arch develop. From the anterior part of the developing head develops the so-called frontal or nasal process, which extends toward the branchial arch. The position of the different processes which take part in the development of the face—the unpaired nasal process, the paired maxillary and mandibular processes may best be seen in embryological models. As differentiation proceeds the nasal process becomes divided into the mid-nasal and lateral-nasal processes and the median process is still further divided by a median incisure into the processes globulares. The median incisure is permanent in many mammals, giving rise to the median fissure, the harelip in the strict sense.

In man the term harelip is applied to fissures or clefts occurring about the upper lip. Strictly speaking, the term should be applied only to the median clefts, and the term lateral clefts should be applied to the deformities or malformations which we commonly see, which are due to failure of the mid-nasal and lateral-nasal processes to fuse. The groove or furrow between these processes normally closes almost completely, only the upper part remaining as a part of the nasal cavity.

The ophthalmonasal fissure is found between the lateral nasal process and the maxillary process of the first branchial arch. If fusion fails here the deformity is an oblique facial cleft.

The space between the maxillary and mandibular processes of the first branchial arch usually disappears as a result of fusion. If fusion fails to occur the deformity is a transverse facial cleft extending outward from the angle of the mouth.

Two different theories have been advanced concerning the fusion of the different processes and their relation to the development of hare or cleft-lip. These are largely of academic interest. It is well to remember, however, that the deformity as it appears in many children is laterally placed and does not correspond to the median fissure observed in some animals, especially the hare.

If the palatal processes of the maxillary portion of the first branchial arch fail to unite or fuse, cleft-palate results. Nothing very definite is known concerning the causes which lead to this failure of the two processes to meet. His made an interesting observation in this connection in one of the early embryos studied by him. Normally the tongue in the developing embryo lies with the nasal cavity. As development proceeds the tongue recedes into the mouth, thus permitting the palatal processes to meet. In the embryo just mentioned the tongue was obliquely placed so that it could not pass from between the palatal processes, and thus formed a mechanical block to their fusion. How often this mechanism is a cause of cleft-palate is not known, but it may be a more common factor than is generally supposed.

Branchial Arches and Grooves.—At an early stage in embryonic life (embryo measuring from 2 to 4 mm.) peculiar structures appear in that portion which later becomes the head and neck. Failure of these to pass through a complete cycle of development may lay the foundation for the development of congenital fistulas or of cysts which may develop in childhood or in adult life.

In an embryo measuring 2.15 mm. two depressions such as those mentioned above are seen. Later a third and fourth appear. The first elevation is on the cranial side of the first depression. The elevations are the branchial arches, the depressions the branchial grooves; sometimes incorrectly spoken of as the branchial slits. These are also seen on the interior of the larynx, the portion of the wall corresponding to the groove being much thinner than that corresponding to an elevation.

The four arches grow successively smaller from above downward and in embryos measuring 9 to 10 mm. the third and fourth arches have already sunk inward, causing a depression known as the precervical sinus. Soon the second arch enlarges and overgrows the sinus, fusing with the underlying arches to fill up the depression of the precervical sinus.

The ventral part of the first fuses with the ventral part of the second arch across the ventral part of the first groove. The dorsal part of the first groove remains as the external auditory meatus, the middle ear and the eustachian tube. The posterior parts of the first and second arches form the concha.

Peculiar infoldings of the skin in front of the ear, giving rise to dermoids or to discharging sinuses, may occur as the results of imperfect development of these parts.

The part which the first arch takes in the development of the lower part of the face has been mentioned above.

The branchial clefts have an especial interest because failure in normal development may lay the foundation for the development of cysts in the neck or of fistulas which may be complete or incomplete.

The second groove from which branchial cysts and fistulas most often develop has permanent remains in the adult—the supratonsillar fossa and the fossa of Rosenmüller. The sinus pyriformis is the remains of the third groove, while a fascial space along the glossopharyngeal nerve is supposed to be the remains of the fourth groove.

Fistulas of the neck have been divided into median and lateral. As far as genesis is concerned these have nothing in common. The middle thyroid lobe is developed as an epithelial evagination of the mouth cavity, the fetal remains of this evagination being represented by the foramen cecum. The thyro-glossal duct extending from the base of the tongue to the isthmus of the thyroid develops from this epithelial evagination. It has been amply demonstrated that median cervical fistulas and cysts develop from this duct. The fistulas are usually incomplete internally, thus accounting for the fact that such fistulas are not usually congenital. A cyst forms at first which either opens spontaneously or is incised. The opening is generally in the median line of the neck, situated between the hyoid bone and the jugulum. The external opening may be very small. The edges may be elevated. Mucus is discharged from the opening.

Such a fistula passes over the incisure of the thyroid cartilage, the thyro-hyoid ligament, in front of, through or behind the body of the hyoid bone, up to the foramen cecum. The fistula is lined by ciliated and squamous epithelium. Mucous glands and lymphoid tissue are found in its walls.

Lateral cervical fistulas—sometimes called fistulas of the thymopharyngeal duct—have an entirely different origin. These fistulas result from anomalies in development or failure in disappearance of the branchial grooves. The external opening of these fistulas is generally found between the anterior border of the sternocleidomastoid muscle and the median line, most frequently just above the sternoclavicular joint. Many times, however, they are found above in the region of the thyroid and cricoid cartilages or the hyoid bone. The opening is usually very small, admitting only a very fine probe.

The internal opening of these lateral cervical fistulas usually lies near the supratonsillar fossa or the fossa of Rosenmüller, which fossæ are the remains of the second groove, or near the sinus pyriformis which is the remains of the third groove. The findings in cases which have been studied during operation or at necropsy show that the fistula passes through the subcutaneous tissues, the platysma and superficial fascia running parallel to the sternocleidomastoid muscle in the deep fascia over the sternohyoid and thyroid muscles to the great wing of the hyoid over the beginning of the internal carotid artery, between it and the external carotid, and finally beneath the digastric muscle to pass into the lateral pharyngeal wall. The fistula is crossed by the styloglossus and pharyngeal muscles. The glossopharyngeal and hypoglossal nerves lie below the fistula.

These fistulas may be complete or have but a single opening. If the opening is single, the fistulas are designated as incomplete external or internal fistulas, depending upon whether the fistula opens upon the skin or the pharyngeal wall.

Cysts of the Neck—Congenital and Appearing in Childhood.—If the thyroglossal duct ends blindly a cyst may form. Such a cyst is situated in or near the median line of the neck. The median cysts lie above or below the hyoid bone or between the thyroid cartilage and jugulum. They vary in size but usually do not exceed a hen's egg in size. They are usually ovoid and elastic. The lateral or branchial cysts lie most frequently between the larynx and sternocleidomastoid muscle; more rarely between the mastoid process and the hyoid. Sometimes they are found in the lower part of the neck. According to my experience, cysts are most frequently found in the lower and posterior part of the submaxillary triangle. They may develop rapidly and reach a fairly good size; it is then difficult to determine the exact primary site. This region being a common site for these cysts the location usually differentiates them from congenital hygromas, which result from developmental changes in the lymphatics and are found in the lateral part of the neck.

Ranulæ.—Ranulæ may be congenital or appear in infancy, childhood or at almost any age. Several different views obtain regarding the origin of these tumors. They appear as round swellings in the floor of the mouth. A ranula is usually a unilocular cyst. The contents often resemble egg albumin, but sometimes they are greenish, yellow, red or brown in color.

Whether these cysts develop from Bochdalek's glands or from the Blandin-Nuhn (so-called tip of the tongue) gland, from the sublingual or incisive glands or from the ducts of the submaxillary or sublingual glands is still a matter of discussion.

Some ranulæ are undoubtedly lined with ciliated epithelium. When this occurs it is quite probable that the cysts develop from Bochdalek's glands, which are derivatives of the thyroglossal duct, or its mouth portion, the so-called ductus lingualis.

It was thought years ago that ranulæ were most often due to closure of the excretory channel of a mucous gland situated near the tip of the tongue, the Blandin-Nuhn gland. If ranulæ developed from this gland it is quite probable that the cyst would involve the tongue itself, but these cysts as they develop raise and displace the tongue without invading it. Therefore it seems quite probable that Bochdalek's gland or the salivary glands are most frequently concerned in the development of ranulæ.

STENOSIS OR OCCLUSION OF THE DUODENUM (CONGENITAL DIAPHRAGM OF THE LARYNX)

During the development of the duodenum the future lumen is occluded by an epithelial plug. This is sometimes spoken of as an epithelial concrescence. This same process occurs in the larynx. As the epithelial concrescence in the duodenum and larynx are quite similar they might well be discussed together.

Roth first called attention to the fact that the masses forming the laryngeal anlage were, in certain stages of their development, united to each other by epithelium. He described this epithelial concrescence as not being limited to the aditus laryngis but extending as far caudalward as the future rima glottidis, even as far as the beginning of the trachea. In his desription he mentions a small space in the posterior part of the epithelium which he regards as the beginning of the laryngeal cavity. He also describes small accessory openings which by confluence become larger and result in the formation of a lumen. The disappearance of the epithelium begins dorsally and extends toward the anterior or ventral surface of the embryo.

As mentioned above, a similar epithelial concrescence has been described in the duodenum by Tandler. This concrescence is especially well marked in the first portion of the duodenum. The epithelium apparently disappears by liquefaction or a mucoid change.

Failure of this concrescence to disappear gives rise to the congenital diaphragm of the larynx which may be partial or complete. If complete, the child cannot survive unless the diaphragm is ruptured. But few cases of such a diaphragm have been found and described. Failure of the concrescence in the duodenum to disappear gives rise to stenosis of this part of the intestine. The duodenum is the favorite site for occlusion. These changes have been ascribed to a number of diseases; most frequently syphilis is suspected, but undoubtedly congenital stenosis in this region most frequently is caused by failure of the concrescence to disappear, followed by secondary changes in the bowel wall.

Megalocolon.—Hirschsprung in 1886 described a malformation of the large intestine as congenital megalocolon. Different etiologic factors have been mentioned as the cause of giant colon or megalocolon and different pathologic changes have been described. The changes in the large bowel have been regarded as due to a primary dilatation, to narrowing of the lumen resulting from the pressure of a full sigmoid upon the rectum; to valve formation in the rectum, hypoplasia of the elastic elements of the bowel wall, etc.

In spite of the number of cases that have been examined the pathogenesis is not definite.

No changes are found in the small bowel. The large bowel, from the cecum to the rectum, is enlarged and thickened. The thickening of the bowel wall is caused by hypertrophy of the muscular layers, especially of the circular layer. The enlargement increases from the cecum on, reaching its maximum in the transverse colon.

Hyperemia and inflammatory changes are found in the lymph-nodes. The transverse folds in the rectum are well-developed in some cases. In a case examined at necropsy by deJong and Muskens, one of the rectal valves was enlarged and seemed to have interfered with the passage of feces, causing a dilatation of the bowel and a hypertrophy of the smooth musculature of the bowel wall.

In cases of congenital megalocolon the thickness of the intestinal wall varies. The mucous membrane is usually smooth and may be covered by a layer of mucus. Plicas and haustra are not found. The blood-vessels are widely dilated and in some instances, at the point of transition between the rectum and sigmoid, a well-developed valve is found. This valve is found posteriorly and usually on the left. The wall of the rectum may be very thick.

In those instances in which the bowel has not been emptied an enormous quantity of fecal material may be found.

MALFORMATIONS OF THE RECTUM AND ANUS

Up to the fifth week of fetal life there is no external opening for the intestinal and urogenital system.

The lower intestine, which later forms the rectum, ends blindly, being connected above with the allantois which develops from the ventral side. That part of the intestine immediately caudal to the attachment of the allantois becomes dilated to form the cloaca, a blind sac which is separated from the outer surface of the embryo by a cloacal membrane. This membrane is formed above by endoderm, below by ectoderm and between the two is mesoderm. The cloaca later becomes divided into a large ventral part, the urogenital sinus, and a small posterior part from which develops the rectum. A urorectal fold growing in from the sides, fusing at the cephalic end first, fusion proceeding caudalwards, separates the future bladder from the rectum.

At the end of the fourth week the skin at the site of the future anus becomes dimpled or slightly invaginated. When the membrane formed by the skin, mesoderm and mucous membrane is absorbed or disappears the lumen of the bowel opens externally and the anus is formed. The embryologic changes in this part are completed at the end of the fourth month and no malformations can occur after this time.

The deformities which result from failure of the usual embryologic processes may be an *atresia ani*, an *atresia ani et recti*, or an *atresia recti*.

In the atresia ani a depression is found at the site of the anus and a delicate membrane occludes the opening of the rectum. The membrane may be very thin. It may be so thin that the green meconium can be seen through it. This thin membrane may rupture at some point and the meconium pass through a small opening of pin-point size or smaller. Sometimes the meconium canalizes the skin of the raphe of the perineum and is discharged at some distance from the membrane.

In atresia ani et recti neither the anus nor rectum are found. No dimpling of the skin is observed. In some of these cases the pelvis has not gone on to full development.

In atresia recti the invagination or dimpling of the skin to form the anus has extended above the sphincter but the rectum ends as a blind sac at different levels in different cases. The blind end of the bowel may be above at the promontory of the sacrum or extend lower, but a definite mass of connective tissue separates the invagination or dimpling of the skin from the mucous membrane of the bowel.

A number of malformations may occur as the result of interference with or complete development of embryologic processes. The bowel may communicate with the bladder, with the penis or vagina. A number of different malformations have been observed.

MALFORMATIONS OF THE SPINE

The neural tube is formed from a band of ectoderm extending along the dorsum of the embryonic disc. This band becomes thickened and a groove is formed. The margins of this groove gradually grow upward to meet and form the neural tube. The surface epithelium which forms the covering of the body separates from this and pushes across the median line to meet the ectoderm of the opposite side. Failure of fusion of the epithelium may occur at any point or along the entire distance giving rise to different forms of rachischisis or spina bifida.

In a series of 91,600 confinements at the New York Lying-in Hospital there were 59 cases of spina bifida, an incidence of 1 in 1552. Chaussier discovered 22 cases of spina bifida among 22,293 children at the Maternité in Paris and the report of the London Committee on Spina Bifida states that in 1882 there were 647 deaths from spina bifida in England and Wales alone.

Spina bifida may occur anteriorly as well as posteriorly. Posterior spina bifida is by far the most common. A number of different grades or degrees of the malformation are observed. In the most marked forms the child is stillborn.

Rachischisis Posterior.—In rachischisis posterior, in the middle line of the back a defect occurs of greater or less extent. There is a depression which above and below becomes continuous with the vertebral canal. In this depression is a strip of varying width of vascular soft, red tissue which above and below becomes continuous with the substance of the spinal cord.

The area medullo-vasculosa represents the remains of the spinal cord. This area is continuous with a delicate red membrane, the pia mater, which in turn becomes continuous with the skin. In the neighborhood of the skin the pia has the appearance of a delicate white scar and this has been called by von Recklinghausen the zona epithelioserosa. Through this may be seen the ends of the unfused vertebral arches.

If the neural groove becomes converted into the neural tube during fetal life as it does in cases of meningocele and syringomyelocele, the epidermis unites across the median line notwithstanding the defect in mesodermic development. When the groove fails to form the neural tube, as it does in rachischisis and myelomeningocele, the epidermis is wanting at the site of the lesion, and infection followed by death may occur quickly.

Moore, in 1905, collected 385 cases of the malformations under discussion. They were distributed in the different regions of the spine as follows:

Region	Percentage
Lumbar	34.0
Lumbosacral	29.0
Sacral	23.0
Cervical	9.5
Thoracic	4.5

Haenig gives the following classification of these malformations which presents a good idea of the tissue involved in and the pathology of the malformation:

1. Fissure of bone, dura, leptomeninges and spinal cord.
    - (*a*) Without hydrops—
        - Rachischisis posterior $\left\{\begin{array}{l}\text{total}\\ \text{partial}\end{array}\right.$
    - (*b*) With hydrops—
        - Myelomeningocele.
2. Fissure of bone, the dura, leptomeninges and cord closed.
    - (*a*) With hydrops of the cord—
        - Myelo- or syringocystocele.
    - (*b*) With hydrops between arachnoid and pia—
        - Meningocele.
3. Fissure of the bone, cord and skin closed.
    - (*a*) With hydrops of the subarachnoid space—
        - Meningocele.
    - (*b*) With hydrops in the subdural space—
        - Meningocele.

Frazier gives the following very clear and satisfactory description of the different forms illustrating the pathology:

> 1. Meningocele is a protrusion of the dura or both dura and arachnoid through a cleft in the vertebræ; the collection of fluid being in the subdural or subarachnoid space posterior to the cord.
>
> 2. Spina bifida occulta. This is a variety of meningocele, but the hernial protrusion is either small or hidden or lacking. This variety may be slow in development and the symptoms may remain latent.
>
> 3. Meningomyelocele is a protrusion of a defective cord and anterior portion of the pia through a cleft in the posterior part of the vertebral column, dura-arachnoid and pia, the collection of fluid being almost invariably in the subarachnoid space anterior to the cord.
>
> 4. Myelocystocele or syringocystocele is a protrusion of the membranes and the cord. In this variety, however, the collection of fluid is in the central canal of the cord which is greatly distended, the cord substance being atrophied and forming the inner lining of the sac.

In cases of spina bifida occulta it is not at all uncommon to find a definite tumor over the site of the hidden spina bifida. This tumor occurs in the median line most frequently in the lumbar region, and is usually a lipoma or myxoma. A tumor occurring in the middle line, in the sacral region with the characteristics of the tumors above mentioned should arouse suspicion of a spina bifida occulta. A number of pathologic conditions may be associated in the severe forms of spina bifida which encroach upon or involve the cord.

PROLAPSE OF THE ANUS AND RECTUM

Prolapse of the anus, in which the mucous membrane is involved, and of the rectum which involves all of the coats of the bowel, occurs most frequently in children. This is indicated by the statistics of Nopalkow, who found that 70 cases occurred between the ages of 1 and 10, 6 between 11 and 20, and 20 between 21 and 60. When prolapse occurs the mucous membrane or all the coats of the bowel pass out of the anal orifice. The mucous membrane may become ulcerated or greatly reddened and is often covered by a layer of mucus.

The chief etiologic factors in the prolapse seem to be an abnormally deep position of the fold of Douglas; insufficiency of the pelvic floor (of muscles as well as bone); insufficiency of the retentive apparatus of the rectum. Excessive abdominal pressure and pathologic changes in the bowel wall are contributing factors. It has been suggested that imperfect fixation of the intestine giving rise to a dragging weight may eventually cause an atrophy of the levator ani.

UROGENITAL SYSTEM

Congenital cysts of the kidneys are not uncommon. In many instances these cysts do not attract attention during infancy or childhood. The symptoms associated with such cysts are usually those of interstitial nephritis. The symptoms may come on in early adult life and when the general examination is made both kidneys are found enlarged.

These cysts may be so large and numerous as to cause marked atrophy of the kidney parenchyma. In rare instances they are so large that the affected organs fill the greater part of the abdominal cavity.

No entirely satisfactory explanation of the development of these cysts has ever been given. They are not infrequently associated with cysts of the pancreas and liver, which have a similar histologic appearance.

The bladder may present a number of malformations or anomalies. It may be abnormally small due to incomplete or imperfect dilatation of the urogenital sinus. The urachus, that portion of the allantois which extends from the bladder to the umbilicus, may persist in whole or part. If it does not undergo atrophy and the lumen persists in part, cysts which become relatively large may develop in the median line. The umbilical portion of the urachus may persist, giving rise to a discharge from the umbilicus which may be mucoid or, if infected, mucopurulent in character.

Abnormal or anomalous openings of the ureter into the vas deferens, the rectum, vagina or urethra may occur.

Anomalies in development of the external genitalia will be considered in the chapter devoted to diseases of these organs.

Exstrophy of the Bladder.—Fissure of the lower abdominal wall is associated with a very serious malformation of the bladder. The mucous membrane of the bladder becomes continuous with the skin of the abdominal wall at the margins of the cutaneous cleft. The posterior wall of the bladder in cases of exstrophy is exposed. The mucous membrane appears inflamed, often ulcerated and the ureteral orifices, from which urine is almost constantly discharged, are seen on either side of the median line. The fissure associated with the exstrophy usually involves the bones of the pelvis and epispadias is associated with the deformity. This malformation is more common in males than females. No satisfactory explanation of the malformation has been given but influences are at work in early fetal life which lead to imperfect development of the lower anterior abdominal wall.

Testicles.—Testicles may be absent, having completely failed to develop. Usually but one side is affected in this case. Supernumerary testicles may be found. Usually, however, in instances of what are regarded as supernumerary testicles, the supposed third testicle is found upon examination to be a hydrocele of the cord, the hydrocele resembling a testicle in shape and consistency. There are, however, authentic cases in which a supernumerary testicle has been found, tissues from the testicle having been examined.

Misplaced (Ectopic) Testicles.—The testicles, which during early fetal life first lie beneath the kidneys, may not undergo normal descent. We then have to distinguish between retained testicles (retentio testis) and misplaced testicles (ectopia testis). When the testicle is retained it is found some place in the course over which it travels during normal descent. When misplaced the testicle occupies a position outside of the course that it usually travels during descent.

When retained the testicle may be found below the kidney, at the point of division of the common iliac artery; along the linea innominata, on the wing of the ilium; free in the abdominal cavity; at the internal inguinal ring, or in the small pelvis.

In cases of ectopia the testicle may be found in the perineum; in the scroto-femoral region; within the inguinal canal; in the small pelvis or at the root of the penis.

The descent of the testicle normally begins at the end of the sixth or the beginning of the seventh month of fetal life. It is completed at birth. Descent may, however, occur at a later period. Lauenstein has described a case in which descent was completed in a boy 15½ years of age. Neugebauer has collected 38 cases of delayed descent, some of these occurring in patients as old as 25, 33 and 48 years of age.

In Austria from 1870–1872 among 6,142,543 recruits, 14,057 cases of undescended testicles were found (about 0.2 per cent.). Coley found among 14,410 children under 14 years of age, 561 retained testicles (3 per cent.); among 3848 young men from 14 to 21 years of age, 92 (2.2 per cent.); among 37,370 men over 21, 75 cases (6.2 per cent.).

The tunica vaginalis is usually well formed in cases of undescended testicles. The funicular portion of the process may, however, not be obliterated and congenital hernia is, therefore, a frequent accompaniment of undescended testicles. The vas deferens is long and tortuous, the epididymis often appearing as unravelled. The vessels in the spermatic cord are usually shortened. The shortened vessels interfere with or render impossible replacement of the testicle in the scrotum and therefore they usually have to be divided to permit of replacement. Not infrequently a distinct peritoneal scar is found at the internal ring or over the course of the cord just outside of the internal ring. The finding of this scar has suggested to some the possibility of fetal peritonitis being the etiologic factor in the failure of descent of the testicle affected.

Retained and misplaced testicles are usually smaller and softer than normal testicles. Various histologic changes have been described. The canals have been found to be poorly developed and the interstitial cellular substance increased, spermatogenesis reduced and degenerative processes in evidence.

MALFORMATIONS OF THE HEAD

The head during birth may be injured either when the birth is natural or by some such manipulation as the application of forceps. The head of the newborn child reacts differently to injury than does that of the adult and usually the traumatizing force is much different.

The injury of the soft tissues which occurs during birth, the caput succedaneum, is a local edema which forms on the deepest part of the head when it presents, where it is exposed to the circular pressure of the cervix and the structures of the vagina. This circular pressure prevents venous outflow causing edema and some extravasation. In advanced or marked cases the extravasation may occur under the pericranium.

Cephalhematoma, which etiologically follows closely on coput succedaneum, is much rarer than the latter, occurring in 2 in 300 births. The blood which is extravasated lies between the pericranium and skull. The extravasation may occur beneath the pericranium (cephalhematoma). The mechanism which results in the formation of a cephalhematoma is certainly the same as that which causes a caput succedaneum.

Traumatic cephalohydrocele (false traumatic meningocele) is seen occasionally in children. They are usually observed in children from three to four years old; more rarely in older children (12 to 16 years). After a severe injury followed by loss of consciousness, paralysis, etc., a fracture or depression is found. Sometimes there are no immediate symptoms. These usually develop over the parietal bone, sometimes on the frontal or at the junction of the occipital and parietal bones. The swelling which develops in these cases is flat. It fluctuates and pulsates and can be reduced by pressure without giving rise to symptoms of increased intracranial pressure. When aspirated a fluid resembling cerebrospinal fluid is removed. In those cases which have come to necropsy there is a fissured fracture, the fissure being of greater or less extent. The dura and arachnoid are adherent to the edges of the fissure. It has been suggested or demonstrated in some of these cases that a tear or fissure of the brain substance extends into the ventricle and that the escape from the ventricle accounts for the large amount of fluid that collects beneath the skin.

Encephalocele. Hydrencephalocele.—Congenital swellings or tumors are observed in different parts of the skull. These are most frequently found in the occipital region; at the root of the nose; in the parietal suture and the small fontanelle. More rarely they are found in the frontal or parietal bone; most rarely in the body of the sphenoid, along the craniopharyngeal canal.

Those occurring in the occipital region are found either above or below the external occipital protuberance. Those occurring in front are found most frequently at the root of the nose. The projection may occur above the nasal bone or may pass outward near the foramen cecum and the anterior part of the ethmoid.

The meningocele is composed of dura, the prolongation of which without the skull is filled with cerebrospinal fluid or edematous pia mater. The sac may contain portions of the brain which contain fluid or merely portions of brain substance which are not dilated by cerebrospinal fluid. The former is called *hydrencephalocele,* the latter an *encephalocele.* The hydrencephalocele has a much greater tendency to enlarge than has the encephalocele.

Any of the swellings above mentioned may be pedunculated or sessile. In many cases the base of the swelling is broad. This is particularly true of the hydrencephalocele and the encephalocele.

The skin covering any of these malformations may become extremely thinned, so thin as to become almost transparent, and may be ulcerated. When ulceration occurs in the skin, infection of the contents is followed by meningitis. The pathologic changes occurring in the brain are dependent upon the part of the brain involved and whether or not the ventricle enters into the formation of the protruding mass.

The opening in the bone may be small in those cases in which a pedicle is found, or may be quite wide in cases in which the base of the swelling is broad. I have seen a case in which there was practically a vertical diastasis of the occipital bone with a protruding mass having a broad base.

Nothing definite is known concerning the etiology of these malformations. The hydrencephalocele is undoubtedly due to a distention of the cerebral vesicles in fetal life. Their occurrence at certain definite points suggests that they follow definite lines of least resistance as they develop.

CONGENITAL DISEASES OF BONE

Congenital diseases of bone may be due to failure of or imperfect development of bone on the part of the epiphyseal cartilage or periosteum or both. Failure of normal development in the epiphyseal cartilage may give rise to short deformed bones; while abnormal fragility may be the result of imperfect periosteal bone formation. There are a number of factors which may be combined in the production of the so-called congenital diseases of bone.

Osteogenesis Imperfecta.—Osteogenesis imperfecta was described by Vrolick in 1849. A majority of those afflicted are born dead or die soon after birth. The bones are imperfectly developed and often the skull feels like a bag filled with fragments of bone. The base of the skull may be well developed and when the brain is removed, the membranous vertex of the skull falls down upon it. The lower jaw is often extremely soft.

The extremities may be strikingly short in relation to the body; the arms and legs are misshapen. The bones may be bent or broken, the ends of the fragments being felt through the skin.

The majority of these cases die early—some cases have, however, lived three to four months. Extra-uterine fractures occur without any violence, after a false step, even while lying in bed. The skin or superficial structures are apparently sensitive for the child gives evidence of having pains in different parts of the body.

The bones in cases of osteogenesis imperfecta are characterized by marked softness and fragility. The cortical bone may dent upon pressure. Fractures healing with deformities lead to shortening of the bones. The bones might be expected to be of normal length because of lack of change in the epiphyseal cartilage. A hematoma often fails to form at the site of fracture. As previously stated, the base of the skull is usually completely formed. The facial bones are usually cartilaginous. The ribs are thin, narrow and irregularly formed. The nodules on them represent recent or old healed fractures. The osteoblasts have retained their ability to form osteoid tissue. The fibrous, vascular marrow and the character of the osteoblasts suggest that the latter can no longer function normally. A part of the osteoblasts undoubtedly change into osteoclasts.

Idiopathic osteopsathyrosis is probably a late form of osteogenesis imperfecta. In this disease apparently healthy but frail children suffer fractures in early life when but slight force is applied. The fractures give rise to but little pain. Deformed, almost corkscrew-like extremities hang as almost useless appendages from the trunk. The soft bones, which bend easily, resemble those in osteogenesis imperfecta. In this instance, however, the disease appears after the bones are formed, so the broken up, thin bones of osteogenesis imperfecta are not found.

According to some authors osteopsathyrosis is an eccentric atrophy of bone—according to others there are definite qualitative changes in the bone. According to Schuchardt both osteogenesis imperfecta and osteopsathyrosis are due to a periosteal dysplasia, periosteal bone formation being seriously interfered with. The activity of the bone-producing cells of the marrow and periosteum is below normal. The lacunar absorption of bone by osteoclasts is as a rule not increased.

Osteogenesis imperfecta and osteopsathyrosis are probably the same disease. They are related to no other bone disease and are characterized by atrophy and softening of the bone.

Congenital Pseudarthrosis.—This is a localized fragility of bone, the bones of but one extremity being affected. The fracture occurs most usually in the bones of the leg, usually in the lower third, and is usually most frequently noted about the fifth or sixth month. A pathologic fracture occurs and fails to unite even when proper treatment is instituted.

The ends of the fragments become pointed, forming an acute angle, apex directed anteriorly. The foot is in the position of plantar flexion because of the action of the tendo achillis.

In cases in which I have operated, the cortical bone is exceedingly thin and soft, bending easily. In one instance in which I operated for non-union I was compelled to remove the transplant from the anteromedial side of the affected tibia; the transplant could be cut with a knife and wrinkled when an attempt was made to bridge the fracture. The marrow was very fatty.

Scars are often found in the skin at the site of the fracture and it has been suggested that the change in the bone is secondary to amniotic adhesions.

The disease is usually confined to the bones affected, being distinctly localized. The soft bone just above the site of fracture may undergo changes, in which it may become hard and not fracture.

Congenital pseudarthrosis is probably a localized periosteal dysplasia. Endochondral ossification in these cases pursues its natural course, while there are apparently great changes in periosteal bone formation. This may be properly called, I believe, a localized form of osteomalacia.

Chondrodystrophia Fetalis or Congenita.—The majority of children showing this disease of bone are born prematurely, being either born dead or dying soon after birth. The cause of death is unknown. The children which survive fail to develop normally, the skeletal changes being very marked. There is a great disproportion between the length of the trunk and the extremities, and the head, having a hydrocephalic appearance, is strikingly large in relation to the remainder of the body.

A prominent forehead surmounts a small, short, broad face, the nose appearing short and plump because of a flattening and recession of the base.

Kaufmann differentiates three types of fetal chondrodystrophy:

1. A chondrodystrophia malacia in which the cartilages are soft.
2. A chondrodystrophia hypoplastica in which there is a cessation of growth in the epiphyseal cartilages with no longitudinal growth in bone.
3. A chondrodystrophia hyperplastica, in which the epiphyseal cartilages do not ossify, and grow irregularly, forming thick, broad, mushroom-like epiphyses on the short diaphyses.

Different clinical pictures may be presented by the different types but the microscopic findings are, on the whole, of such a nature that the disease cannot be confused with any other.

The most important pathologic changes are found in the epiphyses and epiphyseal cartilages. The cartilage cells in the hyaline groundsubstance are not round but fusiform and narrow. They are irregularly dispersed, a longitudinal arrangement being found only near the perichondrium and the diaphysis. There is no parallel arrangement of the cell columns. In rare instances, however, columns of 4–8–12 cells separated by considerable intercellular substance may be found.

The structure of the diaphysis may vary. In some cases the periosteal bone formation is so marked that the centrally placed cartilaginous bone has almost disappeared. In other cases the bone has spongy characteristics. Near the epiphysis the marrow spaces are narrower and the ossification zone is irregular due to the projection of bony trabeculæ or processes into the spaces containing blood-vessels.

Periosteal ingrowths between the epiphyseal cartilage and shaft are almost a constant finding in chondrodystrophy. The growth and shape of the bone is influenced by such growths. They may be so well developed that they are seen by the naked eye. Sometimes such growths are seen at each epiphysis; sometimes at but one epiphysis. In some instances the periosteal ingrowth is observed in but one bone. When the ingrowth is especially well marked the epiphysis may be almost separated from the shaft. In the malacial and hypoplastic types of chondrodystrophy the periosteal ingrowths are frequently if not constantly present. In the hypoplastic forms they are but rarely observed. Such ingrowths limit naturally the growth of bone. The strands or ingrowths develop from both the perichondrium and periosteum. Blood-vessels are carried in these ingrowths which are the result of an active growth of the periosteum and perichondrium. They are characteristic of the disease, never being found in any other form of congenital or fetal bone disease.

Chondrodystrophia fetalis or congenita is a disturbance in the early formation of cartilage and the skeletal changes are due to a lack of cartilaginous growth and the early cessation of endochondral bone formation.

Harelip, cleft-palate, polydactylism, uterus bicornis, and cystic degeneration of the kidneys occur in this disease.

If the child survives, as it develops the upper and lower extremities remain short, the trunk appearing long and the head large. The upper extremity, because of the relative increase in the size of the head of the humerus, is held away from the trunk. The shortening affects mostly the proximal portions of the extremities, the arm and thigh being shorter than the forearm and leg.

Syphilitic Osteochondritis.—Hochsinger found, in 95 out of 263 children with congenital syphilis, that the first evidences of the disease were found in the bones. The changes about to be described—osteochondritis—are observed in 70 per cent. of the newborn having congenital syphilis. The bones are involved in the following order of frequency—lower epiphysis of the femur, lower epiphysis of the tibia, radius and ulna, and the upper epiphysis of the femur and fibula, more rarely the upper epiphysis of the humerus is affected, and still less frequently the upper epiphysis of the radius and ulna. The lower epiphysis of the humerus is the one least frequently affected.

This process, characteristic of syphilis, may occur in any growing endochondral bone. It is found in the centers of ossification in the vertebræ, in the sternum and tarsal bones. Taylor, Parrot and others observed the same changes in the sternal end of the clavicle and these are observed in syphilitic dactylitis as well.

Ossifying syphilitic periostitis is less frequently observed than syphilitic osteochondritis. The periostitis causes a thickening of the long pipe bones, chiefly in the middle. The coincidence of both changes is but rarely noted. Syphilitic periostitis attacks with about the same frequency and intensity the shafts of the femur, humerus and tibia. The bones of the forearm are less frequently attacked and still less frequently the humerus.

A rather striking picture is found in necropsies on children in whom a syphilitic osteochondritis is found. The epiphysis may be attached to the diaphysis by periosteum only. The periosteum may be continuous at but a few points. When the epiphysis and diaphysis are separated a friable caseous material is found. The concave surface of the epiphysis may be irregularly furrowed. The free end of the diaphysis may have a chewed appearance. Syphilitic granulation tissue invades the epiphyseal cartilage from the marrow of the shaft. This granulation tissue is quite comparable to the half-fluid graulation tissue found beneath the periosteum of the newborn when the seat of this disease. It may lead to a separation of the epiphysis. Together with this degenerative process ending in softening goes an irregular ossification leading to the formation of osteophytes at the periphery and a proliferation of marrow in the center. When separation occurs it is within the cartilage and not at the junction of the bones and cartilage.

Syphilitic osteochondritis occurs in early fetal life, for in cases of miscarriage at seven months the process has been found already far advanced.

Pathologic fractures may occur. Tregnbaw describes a case in which 14 were observed in a 13 months old child. Twelve of these had healed. Spontaneous fractures have been observed at all periods, even in utero. These usually are the result of an osteoporosis occurring in children with congenital syphilis, or as the result of bone changes due to a gummatous periostitis or osteomyelitis.

In the early stages of syphilitic osteochondritis the zone of calcium infiltration is widened and between the cartilage and bone a white or whitish-red line is found, measuring 2 mm. in width. Later the zone becomes wider. The zone of ossification becomes irregular. Islands of cartilage become cut off. The cartilage appears yellow, is soft and the cut surface somewhat gelatinous. The cartilage becomes very vascular and the vessels are surrounded by fibrous connective tissue.

CARTILAGINOUS EXOSTOSES AND ENCHONDROMAS

Cartilaginous exostoses and enchondromas are congenital in origin. They are found, when present, in different long bones, usually being proportionate in size and number to the growth activity of the epiphyseal cartilage. Enchondromas are found most frequently at the chondrocostal junction and on such bones as the phalanges. C. U. Weber's statistics dealing with 126 cases show the following distribution: 77 on the bones of the hands, 18 on the bones of the feet, 8 on the tibia, 4 on the humerus, 3 on the shoulder blades and ribs, 2 on the femur, 1 each on the jaw, the frontal bone, the vertebræ, pelvis and clavicle.

According to Virchow, endrochomas occur most frequently at the points where ossification occurs late and irregularly, as in the spheno-occipital, the ilio-pubic and sacro-iliac synchondrosis—next in order of frequency in the long bones in the neighborhood of the epiphyseal cartilage.

When exostoses and enchondromas occur simultaneously the exostoses usually exceed in number the enchondromas. These have peculiarities in shape and distribution. The cranial bones formed in membranes are spared. These growths have been found on the clivus, about the condyles and in the body of the occipital bone. Exostoses of the external auditory meatus have been described many times.

These growths appear in the metaphyses of long bones, which are often doubled in thickness, as wart-like nodular thickenings or coral-like formations. Some are found in the region of the epiphysis, others in the diaphysis into which they have passed as the bone developed.

Frequently the exostoses have on their free end a cavity filled with fluid. This is a bursa and such an exostosis is called an exostosis bursata. It has been suggested that these develop from the articular cartilage, the bursa being a remnant of the synovial membrane. This cannot be so for these exostoses are often found at considerable distance from the joint. This is particularly true of exostoses occurring upon the bones of the trunks.

DISEASES OF THE DUCTLESS GLANDS

Diseases of the ductless glands are not so common in infancy and childhood as in the adult. The thyroid and thymus glands and the hypophysis may present pathologic processes which are of interest.

Simple goiter is sometimes observed in childhood. The adolescent goiter which appears at puberty will not be discussed because it should be classed with goiters of a later period. Cyst-adenomas and fetal adenomas of the thyroid may be observed and they present histologically the ordinary changes found in such growths in the thyroid gland.

Exophthalmic goiter occurs in childhood. The changes in the thyroid gland consist of a change in the character of the epithelium which becomes columnar in type, of disappearance of the colloid or the formation of a thin granular colloid, and the formation of papillary ingrowths into the acini resulting from the overgrowths of epithelium. It is interesting to note that much the same change has been observed in cretins. They have been noted in the human and have also been studied by Marine in cretin sheep. Such changes occurring in cretins should probably be interpreted as an attempt to produce an excessive amount of a secretion which, lacking in iodin, does not play the physiologic rôle for which it was intended.

The malformations of the thyroid and absence of the gland associated with cretinism will be discussed in another chapter.

Hyperplasia of the thymus is of great interest because of its relation to thymic asthma and status lymphaticus. The enlargement may occur in the length or breadth of the gland and involve either its cortical or medullary portions. A general hyperplasia involving both portions of the gland occurs only in small children. Hyperplasia of the medullary portion is the form most frequently observed. The cells are increased in number. Hassall's corpuscles may be decreased in number but may be more or less enlarged. They are not normal, for the center is composed mostly of a fatty, non-nucleated mass which frequently has a hyaline appearance or is calcareous. A hyperoplastic thymus may reach a relatively large size.

Diseases of the hypophysis are not so frequently observed in infancy and childhood, although the development of fat and genital changes which are not infrequently seen are probably dependent on hypophyseal change.

The hypopysis may fail to develop properly, remaining small. In such cases the sella turcica may remain permanently small. This is not infrequently noted in Fröhlich's syndrome, appearing early. The adenomas associated with acromegaly and dystrophia adiposogenitalis are not frequently observed in infancy and childhood.

Secondary changes may be noted in the hypophysis as the result of an internal hydrocephalus, in which cases the floor of the third ventricle may be distended to form a cyst-like mass pressing upon the hypophysis. Interpeduncular cysts, composed of cells resembling mouth epithelium, are occasionally observed in early life but are uncommon. These tumors, which tend to become cystic, develop from islands of mouth epithelium, which during development have been displaced into the anterior portion of the infundibulum from the craniopharyngeal duct.

TUMORS

Tumors occurring in infancy and childhood have certain peculiarities. Many directly result from anomalies in development. The malignant tumors are usually sarcomas or mixed tumors, many different tissues being found in the growths.

Dermoid tumors are observed on the head, being most frequently noted about the external angle of the eyes and about the ears, where embryologic processes are rather complicated, permitting the cutting off of pieces of epidermis and their development to form dermoid cysts. Dermoid cysts are rare in the abdominal wall. They may be found about the navel. Dermoid cysts are seen in or about the ovary, and the majority of ovarian tumors occurring in children are dermoids. They are also found in the testicle.

In case of the more complex dermoids containing cartilage, muscle, bone, pieces of intestine, etc., it is probable that a fetal inclusion must be considered. In a case recently reported by Montgomery a small but well-formed scapula was found in a cystic tumor removed from the back. In such an instance fetal inclusion is the only explanation which can account for the development of the growth.

Angiomas of the skin occur most frequently about the head. Statistics show that 66⅔ per cent. of all angiomas of the skin occur about the face, the different parts being involved in the following order of frequency: Forehead, cheek, lips, nose, ear, eyelids. It has been suggested that these growths occur most frequently along or about embryonal fissures, being sometimes called fissural angiomas. Statistics do not confirm this suggestion. The worst forms probably do occur most commonly at these points and as they are most frequently reported, the impression has been that these growths may have something to do with developmental changes.

The type of angioma varies. The hemangioma simplex is also known as a telangiectasis. This term does not, however, accurately describe the character of the tumor, for in addition to dilatation of the blood-vessels there is also an actual increase in number. The vessels forming such a tumor are held together by connective tissue. They may extend close to the epidermis and reach into the surrounding fatty tissues, muscle and fascia. They may frequently be combined or associated with other tumors, forming the so-called angiolipoma, fibroma or sarcoma. I have operated on an enormous tumor on the back of a child, situated near the left scapula, which was apparently a combination of a hemangioma and a lymphangioma.

Cavernous hemangiomas are composed of tissue which resembles in structure the corpus cavernosum. Such tumors may develop from the simple angiomas or be primarily of the cavernous type. Such growths are usually nourished by a single artery and discharge the blood into dilated veins. Thrombosis occurring in such a growth may result in its partial obliteration. Thrombi may become calcified and converted into bone, forming the so-called phlebolith. These tumors occur on the tongue, lips and cheek, in the muscles of the calf, the rectus abdominis, the sternocleidomastoid and masseter. Of the abdominal viscera, the liver is most frequently the seat of cavernous angiomas, the tumors occurring as small, multiple growths, which may be discovered during a post-mortem examination. Sometimes, especially in children, these growths may appear as large, occasionally pedunculated tumors. They have also been observed in the spleen, bone marrow, uterus and intestines.

The cirsoid aneurysm (racemose arterial angioma) consists of thickened, dilated, tortuous, pulsating vessels, the arteries supplying the tumor emptying directly into large blood spaces without the intervention of capillaries. These may develop from simple congenital hemagiomas. In some instances these angiomas may develop from a single injury. Such growths occur most frequently on the scalp and face, more rarely in the extremities.

Hemangiomas of the lips may be limited or diffuse. The upper is more frequently affected than the lower lip. Frequently a hemangioma is combined with a lymphangioma. Macrocheilia may be caused by a hemangioma alone. Such a growth may be fairly large at birth but following a trauma the growth may develop rapidly. These tumors may grow very rapidly at puberty.

Congenital hemangioma occur not infrequently on the neck at the hair border in the middle line.

Both simple and cavernous hemangiomas occur chiefly in the skin and subsutaneous tissues of the ear, cheek, nose, eye, lip, trunk, and extremities, and in the mucous membrane of the lips, mouth, tongue, in the muscles, bones, peripheral nerves and viscera, especially in the liver, more rarely in the spleen, kidneys, ovaries, uterus, bladder, intestine, brain and spinal cord and their membranes.

Angiomas are frequently combined with other malformations, such as hypertrophy of the extremities, harelip, and spina bifida.

Lymphangiomas appear as the simple, cavernous and cystic types. The cystic lymphangioma is more frequently encapsulated than the cavernous. Even when processes from the main growth extend into neighboring tissues these are surrounded by a capsule. Such growths consist of single or multiple cavities. They may become as large as a child's head. The favorite site for the development of such growths is the side of the neck, where they may extend from the jaw to the clavicle, from the median line in front to the median line behind. They may occur in the cheek, the axillary fossa, groin and upon the flexor surfaces of the extremities. They are occasionally found in the root of the mesentery appearing as the so-called chyle cysts and upon the anterior surface of the sacrum.

The cavernous lymphangioma occurs most frequently in the cheeks, in the tongue, upon the lips, eyelids and lateral regions of the neck. They give rise to such deforming enlargements as macrocheilia, macromelia and the enlargements of the extremities.

The cystic angioma of the neck (cystic lymphangioma) is of surgical interest. Some of the cavernous lymphangiomas, part of which may be cystic, occur as congenital tumors, enlarging rapidly after birth. I have observed, as previously stated, an enormous tumor on the back which was combined with a hemangioma. Such cysts usually contain a serous fluid which after injury may be mixed with blood. These cysts are lined with endothelium. The wall consists of fibrous tissue, at times rather thick, which is not adherent to the surrounding tissues. Processes may extend from this fibrous wall into and between smaller cysts or cavernous-like tissue. These cystic growths, because of the character of the wall, are usually easily enucleated.

MIXED TUMORS

The group of so-called mixed tumors afford an interesting study. They occur in infancy and childhood and most frequently involve certain organs. Some pathologists believed at one time that these growths developed as the result of a metaplasia or tumor-like metamorphosis of adult tissue. It seems to be quite definitely established at present that these growths arise from misplaced remnants of undifferentiated germinal tissue which may form a part of any one or all of the tissues developing in the region from which the germinal tissue is displaced.

Mixed tumors of the urogenital system are probably of most interest to the pediatrician. These tumors occur most frequently in the kidneys, sometimes being present at birth. Both kidneys may be involved. These tumors grow rapidly. In the beginning they may be surrounded by a capsule, the kidney tissue being displaced and compressed until only a small strip remains, which may be found at the poles. Gland tubules, muscle, bone, cartilage and sarcoma-like tissue may occur in different regions of the same tumor. That the histology varies considerably is indicated by the number of terms that have been applied to these growths, such as adenosarcoma, adenomyxosarcoma, adenochondromyosarcoma, etc. Birch-Hirschfeld gave the name of "embryonal glandular sarcomas" to these growths. The misplacement of tissue must, according to Wilms, occur very early, for the number of kinds of germinal tissue displaced must correspond to the number found in the growth. According to him these tumors develop from islands of germinal mesoderm which are separated and displaced from the neighborhood of the primitive kidney.

Mixed tumors like those just mentioned occur in the vagina of small female children as grape-like growths, which grow rapidly until they fill the vagina, protrude between the labia and extend outward to invade the connective tissues of the pelvis. This type of tumor, composed of many different kinds of tissue elements, also occurs in the testicle, but the testicular tumors are found more frequently in the adult than in infants and children.

Teratomas are composed of highly differentiated tissues which in their development produce highly developed fetal structures. They differ from the teratoid mixed tumors in that the tissues forming the latter have not developed into organs or highly organized structures. Teratomas are closely related to fetal inclusions and are either present at birth or develop soon after. They usually lie near the surface of the body and may occur, for example, about the mouth, being attached to the base of the skull, in the neck or coccygeal region or within the body cavities. These growths never develop from a matrix which is displaced after birth. Fully developed organs, such as head, teeth, a scapula (Montgomery), femur, foot, etc., suggesting fetal inclusions, may be found in these growths.

Albarran and Imbert's statistics show the frequency of occurrence of these malignant tumors of the kidney:

Years	Cases	Percentage
From 0 to 3	80	55.00
4 to 6	42	25.50
7 to 9	21	12.70
10 to 12	7	4.30
13 to 15	6	3.60

Carcinomas are rare in infancy and childhood although, occasionally, undoubted instances of malignant epithelial growths have been reported.

Sarcomas may develop from any tissue. They do not differ histologically from similar tumors occurring in the adult, although they may be characterized by more rapid growth.

Myelomas are most often observed in older people. They do, however, occur in children, developing from the bone marrow. They do not form metastases, but multiple tumors may develop simultaneously in different bones. The adjacent bone is gradually destroyed. The cranial bones,the seat of such a growth, have a peculiar round punched-out appearance. It seems almost as if a sharp, round punch had been used to remove the portion of bone involved. These tumors are often accompanied by fever and a marked anemia. Pathologic fractures of the affected bones may develop. These growths develop from the marrow cells and are considered by some as representing localized hyperplasias of the marrow cells, by others as lympho-sarcomas. Sarcomas of bone appear either as the central giant-cell variety or those which develop from the germinal or from the fibrous layer of the periosteum.

Epulis is a giant-cell tumor characterized by its benignancy. They form irregular growths of a violet-red color, frequently growing into the interval between two teeth, developing between the periosteum and the tooth. How these growths should be classified has been often discussed. They contain numbers of giant cells with many nuclei, and stroma composed of large round cells. After thorough removal they show but little tendency to recur and they do not form metastases. Some regard such growths as inflammatory. Histologically they resemble very closely the central giant-cell sarcomas.

Central giant-cell sarcomas develop in the metaphysis of long bones, although they may appear in the shaft. They usually appear as globular growths which expand the bone asymmetrically and break through on one side or the other to invade the surrounding tissues. They contain large number of giant cells with many nuclei. The cells forming the greater part of such a growth may be round or spindle-shaped and the malignancy depends more upon the character of the cells forming the greater part of the growth than upon the giant cells. The growth may be solid, appearing rather white and fibrous on section or the cells may undergo a fatty change so that a greenish color is imparted to the growth when sectioned. Tumors developing from the bone, which are rapidly growing and composed of small round cells, may contain large blood spaces. Thrills and bruits are often detected in such growths to which the term bone sarcoma is often given.

Osteogenetic sarcomas develop from the germinal layer of the periosteum. The cortical bone is eroded and as the tumor grows stalactite processes of bone are formed which are laid down at right angles to the shaft. This distribution of the stalactite growths is important thing an in regard to *x*-ray diagnosis. Such growths, which are very malignant, may contain giant cells but these tumors do not shown the benign characteristics of the central giant-cell sarcomas which do not produce bone. Sarcomas which develop from the fibrous layer of the periosteum do not differ from small round- or spindle-cell sarcomas developing from fascia or other fibrous tissue. They are rapidly growing tumors composed of small round or spindle cells with little or no stroma. They develop rapidly, form metastases early and are exceedingly malignant.

CHAPTER CLXIV

FETAL MALFORMATIONS

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It is primarily the purpose of this section to deal with those forms of abnormal development which show definite evidence of major embryonic duplication, and which are variously known as polysomatous monsters, double monsters, or jointed twins. While the introductory paragraphs contain some general remarks bearing on the origin and development of other forms of malformations, the detailed accounts of the latter will be found in connection with other sections of this work.

ORIGIN OF DOUBLE MONSTERS

In the vast majority of cases the single fertilized human ovum gives rise to a single individual (embryo or fetus) inclosed in a single chorion. In other and very much rarer instances the ovum forms a single chorion, but inclosed within this membrane is a product of conception which shows evidence of a more or less complete progression towards the formation of two separate individuals from the original single egg cell.

Formations of the latter class show the widest variation in their form and structure. At one end of the scale lie cases in which a single and almost perfect individual includes within it a more or less organized mass in which parts of a second individual may be recognized, or other cases in which the tendency towards duplication may be recognized in the occurrence of supernumerary members or parts. Lying intermediate are the double monsters or conjoined twins, characterized by two more or less completely formed bodies more or less extensively united. And terminating the series are the cases in which the process of duplication is complete, and the ovum has developed two quite separate individuals, true duplicate (monozygotic) twins. All, however, have two fundamental characters in common: They are always surrounded by a single chorion, and the sex (in those cases where recognition of sex is possible) is always the same in both members of the pair.

Modern experimental teratology has thrown much light on the origin of double monsters. The effects of changes in environment are particularly well established by these studies. It has been shown repeatedly that embryonic duplications of all grades and degrees may be produced in certain vertebrate embryos by changes in temperature, by subjection to the *x*-ray and ultraviolet ray, by pressure, by mechanical separation, by changes in the salt concentration and oxygen content of the surrounding medium, and by a number of other experimental procedures. These experiments have brought out clearly the fact that the modification in development is determined not by the nature of the force which is brought to bear on the developing mechanism but by the stage of development reached when this force is applied. Various forms of insult offered to the embryo at a given time will produce the same form of developmental arrest or perversion while the same form of stimulus applied at different times will cause quite different forms of monstrosities. This evidence supports the conclusions of Mall[22] that uterine disease and faulty implantation play a large part in the production of pathologic embryos and malformations in the human embryo.

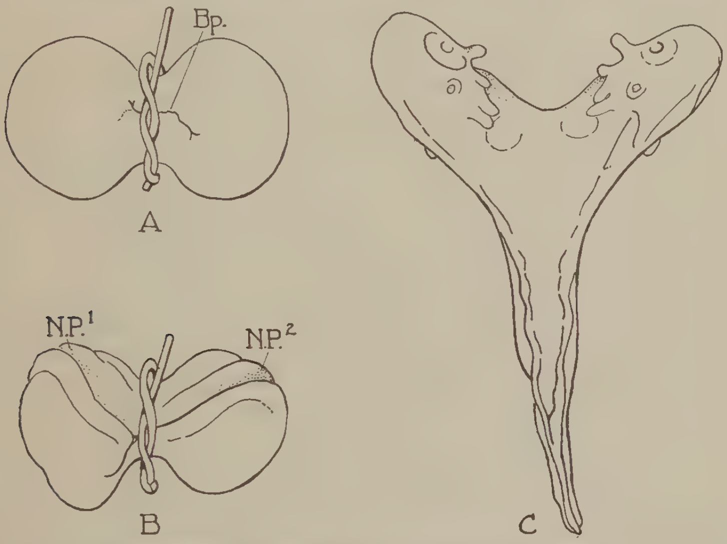

Fig. 97.—Three stages in the artificial production of a double monster by strong median constriction, with a fine hair, of the egg of a triton (newt). *Bp.*, blastopore; *N.P.*, neural plates. (After Spemann,[35].)

The chief evidence which can be advanced for the germinal origin of embryonic duplications seems to be as follows.* First, the frequency of occurrence of double monsters in general and of the several varieties differs noticeably in different species of animals. In some of the lower forms the occurrence of embryonic duplications is quite common, while in other related species it is rare. Second, in at least one mammal, the armadillo, the offspring are invariably same-sexed quadruplicates inclosed in a single chorion and are the product of a single ovum so that it is evident that embryonic duplication is the rule in this species. Third, the statistical studies of Davenport[12] show that human monozygotic or duplicate twins are more common in some families than in the general population, and that the tendency towards this peculiarity is carried down through both the male and the female offspring. This evidence regarding the frequency of duplications in certain families or species does not, however, necesstiate the assumption that the abnormality is a directly inherited one for, as Stockard has pointed out, it is possible that the type of organization of the ovum may render it particularly liable to the action of developmental arrests without the assumption of a true germinal peculiarity in this regard. In the case of the armadillo it has been found that the ovum of this animal normally passes through a long inactive period in the uterine cavity before implantation, and it is in all probability this phase of developmental quiescence which is responsible for the polyembryony of this species. It may be remarked that there seems to be no reported case of a woman having twice given birth to double monsters, although there are many cases in which the birth of such a monster has been preceded or succeeded by normal births.

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* This remark applies only to polysomatous monsters. The germinal origin of many malformations, as, for example, brachydactyly, syndactyly and polydactyly, seems very definitely proven.

Taken as a whole it seems that the opinion advanced by Mall[22] a number of years ago that "all of our experience in teratogeny, if read aright, indicates that the normal ovum got into a diseased uterus, did not implant itself well, and the consequent impairment of nutrition produced a monstrous embryo" is the most rational one at the present time.

The time of development of embryonic duplications in man has not and probably never will be definitely established, but we may draw some conclusions on the subject from the experimental evidence furnished by lower forms. Early observers encountered germinal discs showing the formation of two individuals in progress, and they concluded that this development was a fairly late one. Later it was shown that in certain lower forms various types of embryonic duplications might be produced at will by a number of experimental procedures which involved the separation of the two blastomeres formed by the first division of the fertilized ovum; and it was argued that all duplications could be traced to this first division of the developing organism. But more recent experimentation has shown that this is not necessarily the case. In certain species of animals the separation of two blastulæ does not result in the formation of two complete individuals, thus indicating that the developmental substance is already partially segregated in one or the other blastomeres. In others it is possible to produce double forms by experimental interference at a much later time in the blastula or early gastrula stage.

A very enlightening piece of evidence on the time of embryonic duplications in mammals is furnished by the embryology of the armadillo which has been studied in great detail by Patterson and Newman.[25,26,27,28] The North American species of this animal gives birth to four same-sexed and monochorionic young at a litter. This peculiarity suggested the possibility, later shown to be a fact, that the embryos all arose from a single fertilized ovum. The process of differentiation is illustrated semi-schematically by Fig. 98*A* to *F* inclusive. Figure 98*A* shows a portion of the blastodermic vesicle with the inner cell mass which will give rise to the embryos, attached to its inner surface. Figure 98*B* is a somewhat later stage showing a little more differentiation of the inner cell mass. In Fig. 98*C* this mass has formed a ball of cells which is being hollowed out to form the amniotic cavity. A later stage in Fig. 98*D* shows the completely formed amniotic cavity from the floor of which the embryos will develop. At this stage no separate embryonic fundaments can be recognized. In Fig. 98*E* two of the four embryos are indicated as distinct thickenings of the floor of the amniotic cavity and in Fig. 98*F* these masses appear as cross-sections of

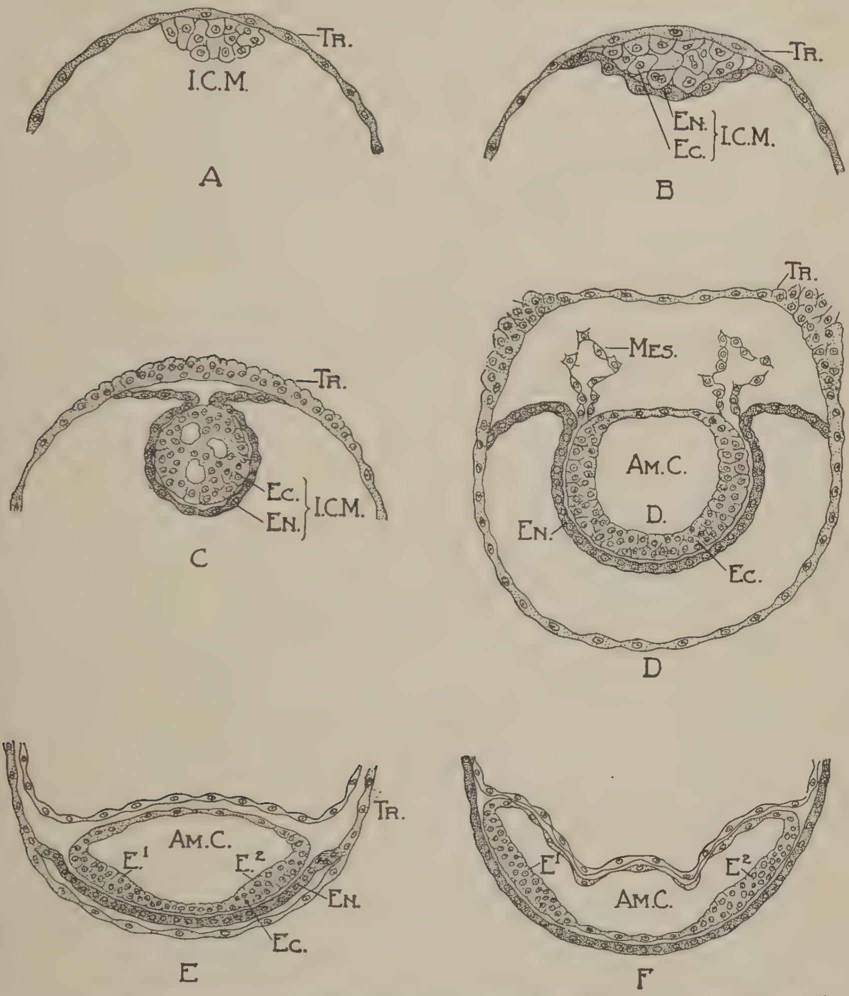

FIG. 98.—Six semischematic sections of the germinal vesicle of the armadillo showing stages in the development of twin embryos. *Am.C.*, amniotic cavity; *D*, germinal or embryonic disc; E^1 and E^2 forming embryonic shields; *Ec.*, ectoderm; *En.*, entoderm; *I.C.M.*, inner cell mass; *Mes.*, mesoderm; *Tr.*, trophoblast. The figure is described in more detail in the text. (After Newman,[17].)

definite embryonic shields and the portion of the embryonic disc separating them has been reduced to a single layer of flattened cells.

If the formation of major embryonic duplications takes place in the human ovum at the stage when it is most usual in other higher forms it may occur sometime before the close of the second week following fertilization, possibly in the latter half of this period.

At one time teratologists were sharply divided into two schools on the question of the mechanism of formation of double monsters. One group maintained that duplications were produced by the fusion of two embryonic fundaments originally discrete, while the other held that they arose by the splitting of a single germ. This controversy loses much of its significance in the light of modern embryological investigation. In the genesis of the symmetric types of double monsters there is, no doubt, a formation of two embryonic fundaments, each with its own body-axis, but these are probably partially fused from the first, the degree of overlapping depending on the position of the two germs on the developing embryonic disc. The more complete forms of asymmetric monsters and certain teratomata probably have a similar origin but in these cases the development and differentiation of the smaller component has been inhibited by the growth of the larger. The reader is recommended to the recent monograph of Stockard[36] for a general consideration of this subject.

CLASSIFICATION OF EMBRYONIC DUPLICATIONS

Since the various forms of human double monsters which have been described are to be regarded only as examples of a continuous series of possible varieties it follows that any attempt to classify them is somewhat arbitrary and only partially satisfactory. Among the more important of these classifications are those of Geoffroy Saint Hilaire,[15] Förster,[14] Ahlfeld,[1] Taruffi,[38] and Ballantyne.[2] An excellent summary of these schema with a comparative table of the portions of them dealing with symmetrical double monsters will be found in Schwalbe.[34] A later classification, as developed by Schwalbe on a purely morphologic basis, is given below in abbreviated form and with a few minor modifications. This classification is followed in the descriptions of the subsequent pages.

I. Free monozygotic twins.
  1. Symmetrical (*Duplicate* or *identical twins*).
  2. Asymmetrical (*Acardii*).
    (*A*) Forms in which the development of the less perfect individual is much reduced but in which the body form and the various parts may still be recognized (*Hemicardius*).
    (*B*) Forms in which a large part of the body (either cranial or caudal) is lacking in the less perfect individual.
      (*a*) Cranial part lacking (*Holocardius acephalus*).
      (*b*) Caudal part lacking (*Holocardius acormus*).
    (*C*) Forms in which the general body form and the various parts of the less perfect individual are wholly unrecognizable (*Holocardius amorphus*).

II. Joined twins or double monsters proper.
  1. Joined twins in which both individuals are equally developed.
    (*A*) Forms united in the frontal plane of the body and organized symmetrically thereto.
      (*a*) Forms united ventrally.
        (*a′*) Supra-umbilical union.
          1′. Complete supra-umbilical union (*Cephalothoracopagus*).
          2′. Incomplete supra-umbilical union (*Prosopthoracopagus, Thoracopagus, Sternopagus, Xiphopagus, Craniopagus frontalis*).
        (*b′*) Infra-umbilical union and supra- and infra-umbilical union (*Ileoxiphopagus, Ileothoracopagus, Cephalothoracoileopagus*).
      (*b*) Forms united dorsally (*Pygopagus, Craniopagus occipitalis*).
    (*B*) Forms united in the transverse plane of the body and organized symmetrically thereto.
      (*a*) Cranial union (*Craniopagus parietalis*).
      (*b*) Caudal union (*Ischiopagus*).
    (*C*) Forms which are in part double and in part fused in the median sagittal plane of the body.
      (*a*) Forms double cranially (*Duplicitas anterior*).
      (*b*) Forms double caudally (*Duplicitas posterior*).
      (*c*) Forms double caudally and cranially but united in the trunk region (*Duplicitas media*).
  2. Joined twins in which the two individuals are unequally developed (*Autosite and parasite*).
    (*A*) Less developed individual (parasite) attached to the head region of the more developed (autosite) (*Craniopagus parasiticus, Janus parasiticus, Epignathus* and related forms).
    (*B*) Parasite attached to the neck, thorax or abdomen of the autosite (*Thoracopagus parasiticus, Epigastricus*).
    (*C*) Parasite attached to the pelvic region of the autosite (*Ischiopagus parasiticus, Pygopagus parasiticus*).

DESCRIPTIONS OF THE SEVERAL VARIETIES OF EMBRYONIC DUPLICATIONS

As will be noted from the preceding outline, embryonic duplications may be divided into two general classes, the free monozygotic, in which the duplication is complete resulting in two separate individuals inclosed in common fetal membranes, and those in which there is an incomplete division with persistent direct body union.

Free Monozygotic Twins

The first class, the free monozygotic twins, are divided into two groups, symmetrical (duplicate or identical twins) and asymmetrical.

Symmetrical Free (Duplicate or Identical) Twins.—Duplicate twins, while not commonly regarded as malformations, are in their genesis the most complete example of the process of embryonic duplication. These forms are always inclosed in a single chorion and possess a single common placenta. They are always same-sexed. It is probable that male sets of duplicate twins are slightly more common than female, although the statistics on this subject seem in most cases to be deduced from a study of the frequency of both monozygotic and fraternal twins and are therefore possibly misleading. It has been estimated that approximately one-fourth of all human twins are of monozygotic origin.

The common observation of the remarkable similarity of duplicate twins is borne out in the main by modern anthropometric studies, and the slight differences in size and form which are encountered may be attributed to modifications in the post-natal environment. Wilder's[46] extensive study on this subject shows that this similarity extends in a marked degree even to such minutæ as the general patterns of the friction ridges on the palms and soles.

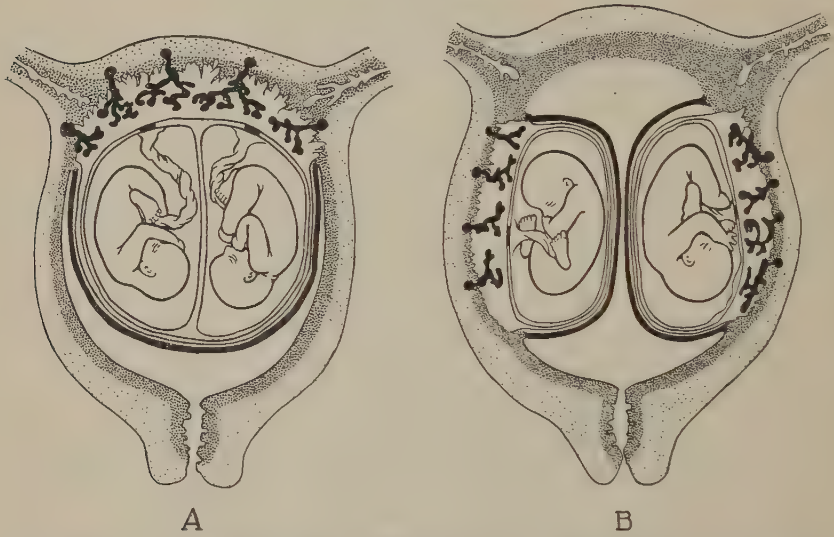

Fig. 99.—A comparison of the fetal membranes of duplicate (monozygotic) and fraternal twins. *A*, duplicate twins enclosed in double amniotic membranes and a single chorion and decidua. *B*, fraternal twins enclosed in double amniotic and chorionic membranes and double deciduæ. In some cases, the deciduæ and chorions may be single but the amnionic sacs are always double. (After Kollmanm.)

Acardii.—The second class of free monozygotic twins includes those cases in which one member of the pair is a normal or nearly normal individual while the other is represented by a mass, sometimes showing certain features of body form and sometimes quite amorphus, which is known as an Acardius. In all such cases the vascular systems of the Acardius and the more normal fetus are always connected and the propulsion of the blood through the united systems is accomplished solely by the heart of the more perfect twin. An anatomic

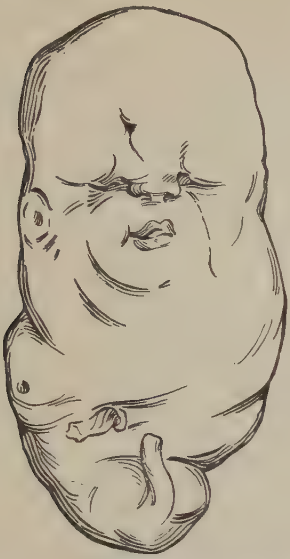

FIG. 100.—Holoacardius acormus. (After Cerf,[9].)

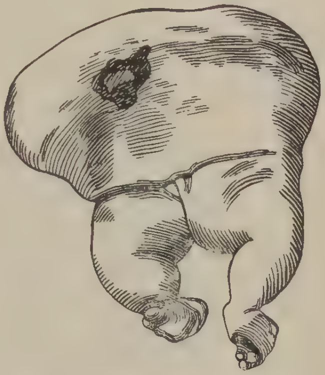

FIG. 101.—Holoacardius acephalus. (After Licht and Calicchio,[21].)

structure representing the heart may be present in the Acardius (and to this extent the name is a misnomer) but it is not functional. Generally each member has a separate umbilical cord attached to a single common placanet where the vessels anastomose; although, in rare cases, the Acardius is attached directly to the placenta. Usually Acardii have a single umbilical artery.

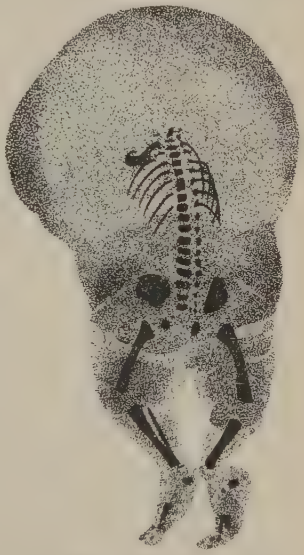

FIG. 102.—Radiograph of the specimen shown in Fig. 101. (After Licht and Calicchio,[21].)

Acardii are rather arbitrarily classified according to the perfection of their body form and the development of the vascular system. Those having the general outlines of the entire body and a rudimentary heart are termed Hemicardii (Acardius anceps). Those in which a large cranial or caudal portion of the body is missing and in which there is no trace of a heart, are classified as Holoacardius ancephalus and Holoacardius acormus. The former variety in which the cranial part of the body is absent is much the commoner of the two. The external body form of a recently described example of this variety is shown in Fig. 101; and Fig. 102 is a tracing of a radiograph of the same specimen. The external appearance of a rather typical example of Holoacardius acormus is shown in Fig. 100.

Specimens of Acardii which appear only as disorganized masses of tissue are termed Holoacardius amorphus. The external appearance of one of these is shown in Fig. 103, and Fig. 104 is a sagittal section of a similar specimen. It may be noted that while this figure as well as Fig. 103 shows a great general disorganization of the body form and structure, certain related parts which correspond very closely both in form and size with those of normal fetuses of the same age. The ossification of the tarsus in Fig. 101, for example, is practically identical with that usually found in fetuses of this size.

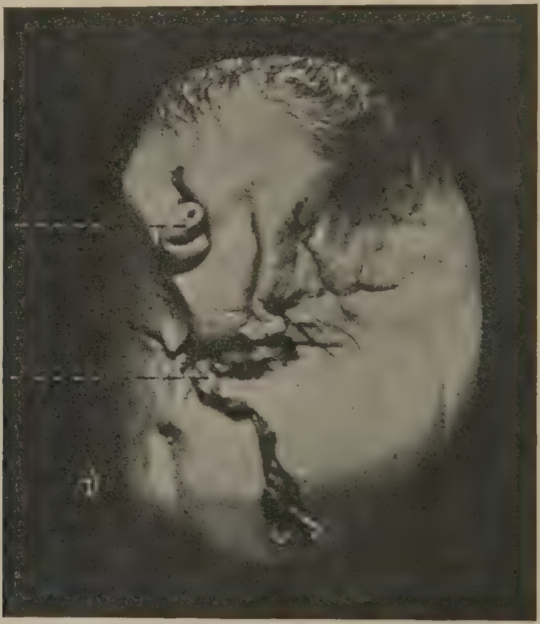

Fig. 103.—Holoacardius amorphus. (After Broman,[8].)

Our knowledge of the genesis of Acardii is still in great confusion. The hypotheses of von Winckel and others that these malformations arise through amniotic constrictions may be safely rejected, at least for the great majority of cases. The theories proposed by Ahlfeld[1] and Shatz[33] postulate the complete establishment of a separate circulation in each of the developing twins and a subsequent taking over of both circulations by the stronger, better placed, and better nourished individual, with resulting degenerative changes in the weaker one. However, the developmental defects of these specimens seem too profound to be explained on the basis of a secondary modification of the circulation alone, and, as suggested above, they present a picture of disorganization rather than degeneration. To the writer it appears much more probable that these circulatory defects are but part of the general primary perversion of development in these forms—a perversion which probably leads to the early death of all specimens of this kind with the exception of those few cases in which a chance functional connection with the circulatory system of the sound twin permits their existence for the remainder of prenatal life.

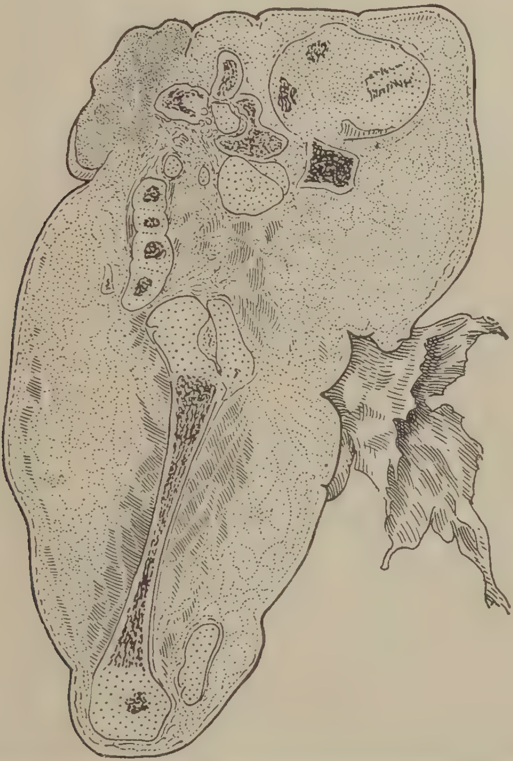

Fig. 104.—Longitudinal section of a Holoacardius amorphus. (After Schwalbe,[34].)

JOINED TWINS OR DOUBLE MONSTERS PROPER

True conjoined twins or double polysomatous monsters consist of two components more or less completely united, each of which shows some of the characteristics of a separate individual. They are classified in two main groups: First, the symmetrical forms in which the components are usually approximately equal in size and development; and, second, the asymmetric form (autosite and parasite) in which one small and incompletely developed component is attached to a much larger and more completely developed one. This classification is not an entirely satisfactory one since transitional forms between the two categories occur in both animals and man.

SYMMETRICAL DOUBLE MONSTERS

The symmetrical double monsters may be arranged in three groups on the basis of the union of the paired components in the frontal, the transverse, or the sagittal body plane. Wilder's diagram, which is reproduced in Fig. 105, illustrates most of the types of this class of abnormalities.*

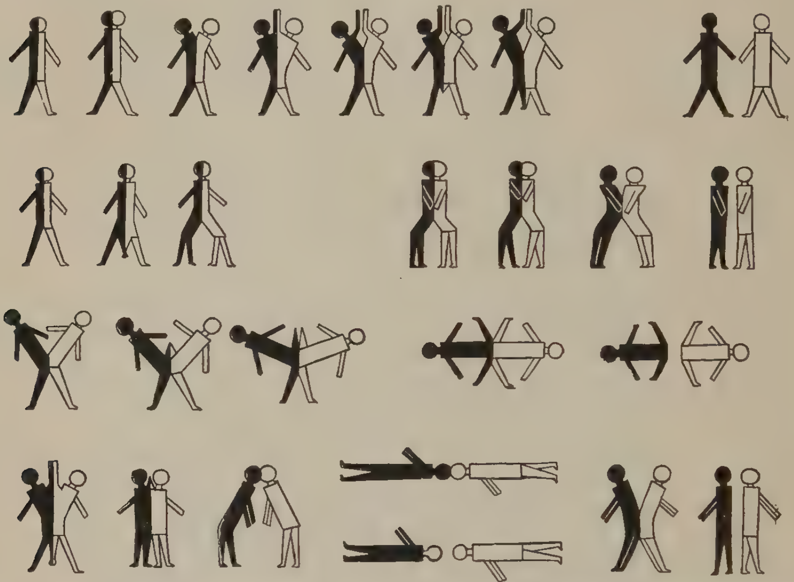

FIG. 105.—A diagram illustrating the principle forms of joined symmetrical twins. (After Wilder,[46].)

Forms United in the Frontal Plane.—These forms of symmetrical double monsters are divided in two sub-groups, those with ventral and those with dorsal fusion. The first group is subdivided on the basis of the location and extent of the area of fusion: A classification of convenience only, there being numerous intermediate forms. The more important types are briefly considered below.

Cephalothoracopagus (Janus, Janiceps, Syncephalus).—In these forms the fusion of the two components in the frontal plane extends from the crown to the middle abdominal region, and the umbilical cord arises from the inferior margin of the connecting mass. Two varieties are recognized. In Cephalothoracopagus disymmetros the two components are united squarely in the frontal plane thus forming a body which presents two broad anterior surfaces and two narrow posterior ones. The common head produced by this union bears two faces, one of which is formed from the right half of the facial region of the first component and the left half of the facial region of the second, while the other face is formed from the left half of the facial region of the first component and the right half of the facial region of the second. There are two cerebra which may be lightly joined at the frontal poles. There are also two hypophyses; two cerebella, each representing the complete cerebellum of one of the members of the monster; two brain stems; and two spinal cords. The thorax presents two anterior surfaces each composed, as in the case of the faces, of the right half of the anterior part of the chest of one component and left anterior half of the chest of the other. The heart is duplicated, one organ lying towards one anterior chest surface and the other towards the second anterior surface.

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* In this and the following descriptions the terms union, fusion and the like are used in a descriptive sense only, and do not imply the actual joining together of two distinct embryos during their development.

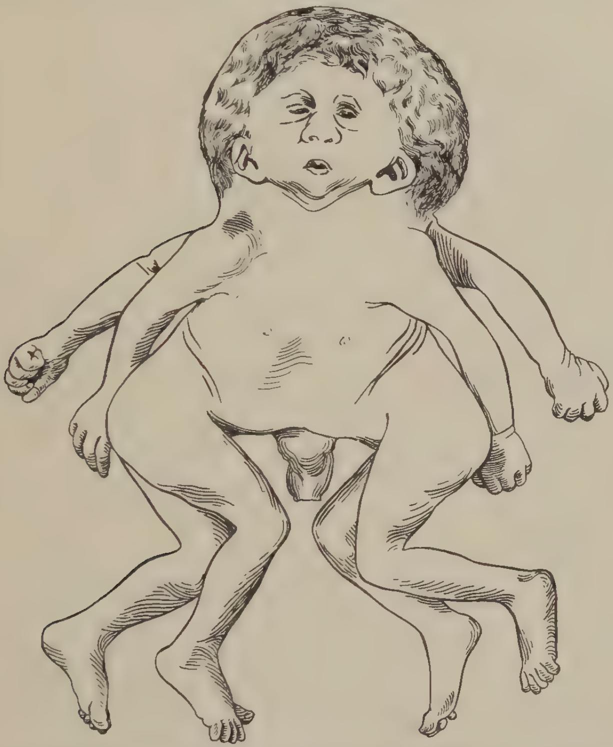

Fig. 106.—Cephalothoracopagus monosymetros. View of completely formed anterior surface. (From a specimen in the Anatomical Collection of the University of Minnesota.)

In the second variety, Cephalothoracopagus monosymmetros, the fusion of parts is still symmetrical but has proceeded much farther on one aspect than the other so that a complete face, formed from the right and left facial regions of the two components, is found on one surface while the other bears only the rudiment of a physiognomy. The cerebrum in these forms is more fused than in the disymmetric ones and the hypophysis is usually single. There are two separate spinal cords and cerebella. The heart on the side of least fusion is usually well developed while that on the side of more complete fusion is rudimentary. The digestive tubes are fused into a single tract to the level of the origin of the yolk-sac stalk from the small intestine and are double below this point.

The monosymmetric variety of Cephalothoracopagus is less rare than the disymmetric form. Outline drawings of a typical example of Cephalothoracopagus monosymmetros are shown in Figs. 106, 107.

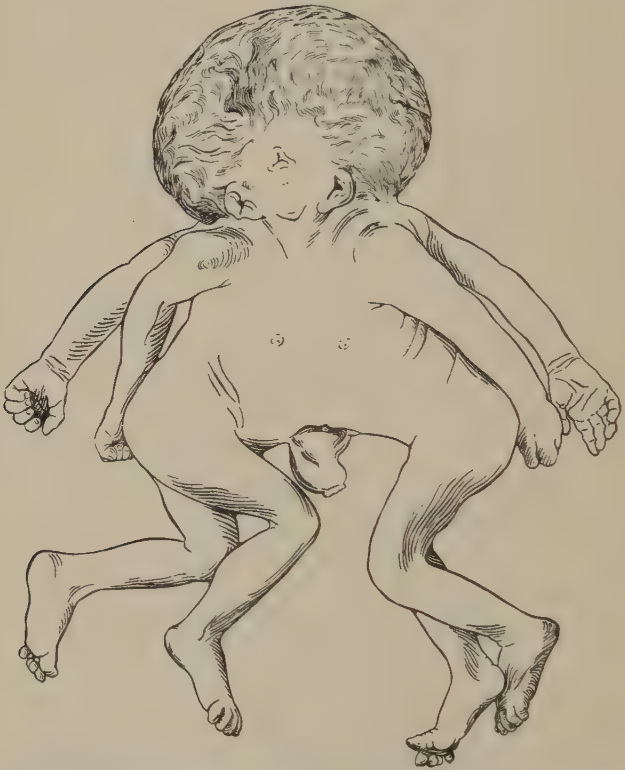

Fig. 107.—Cephalothoracopagus monosymmetros. View of the secondary, incompletely formed, anterior surface of the specimen shown in Fig. 106.

Prosopothoracopagus.—This is an extremely rare variety, intermediate between those described above and those following, in which the union in the ventral frontal plane extends from the oral region to the level of the umbilicus, or, in some cases, throughout the abdominal region.

Thoracopagus, Sternopagus, Xiphopagus, Sternoxiphopagus.—Under these terms is included a series of cases characterized by ventral union of the upper part of the trunk in the frontal plane. The exact region of the union is indicated by the prefix of the name applied to each variety.

The internal anatomy of these forms varies greatly with the degree of union, and the more completely fused varieties may be either monosymmetric or disymmetric. The heart may be double, single, or double with communicating passages. In the cases of more complete union the intestinal tracts are usually joined in a single tube in the region of the point of attachment of the yolk-sac stalk, parts of the two ileii forming a common intestine. Above and below this segment the two tracts are separate. In many cases, however, the two canals are separate throughout. In all except the most lightly joined forms the livers are more or less completely united by a bridge of hepatic tissue, which often contains large anastomosing vessels. In the more completely fused examples there are common pleural, pericardial, and peritoneal cavities; but in the more lightly joined specimens the communications between these respective cavities are reduced to narrow canals or, in very rare instances, are entirely absent.

Practically all specimens of this group show some skeletal union between the components. In the disymmetric forms of Thoracopagus there are two compound anterior thoracic walls, including two sterna, each formed from the right half of the thorax of one twin and the left half of the thorax of the other. In the less completely fused specimens the two sterna are simple and are connected by a common xiphoid process, or the union may be reduced to a slender cartilaginous bar uniting the lower ends of simple xiphoid processes.

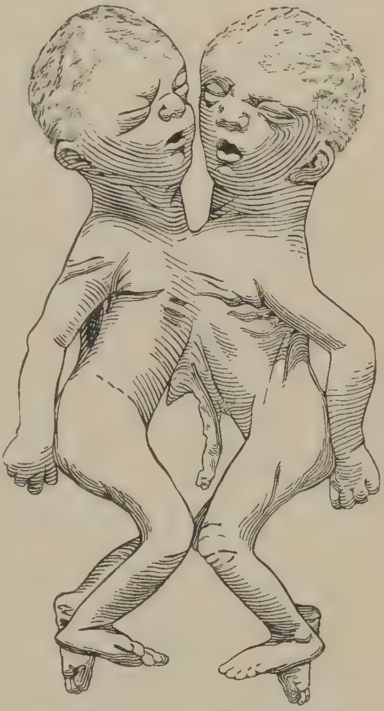

FIG. 108.—Thoracopagus. (After Hirst and Piersol,[18].)

In the forms with least union, the connection between the components represents merely a reflection of the anterior wall from one twin to the other. It contains the cartilaginous bridge between the xiphoid processes, some muscle and fibrous tissue and the umbilical structures which pass from the two abdomens to a common funis arising from the lower surface of the connection.

The different varieties discussed above form the commonest type of double monster in the human species and are most capable of surviving in post-natal life. A discussion of their viability and the possibility of surgical separation will be found in another part of this section.

Ileoxiphopagus, Ileothoracopagus.—These are forms in which the area of frontal fusion extends from the ventral surface of the pelvis to the lower or upper margin of the thorax. Both monosymmetric and disymmetric varieties have been described. Some specimens have four arms and four legs, but in others the upper or lower extremities may be represented by three limbs, the middle one being a compound structure formed by the fusion of the limb elements of both components. The viscera are extensively fused. These forms are not viable.

Pygopagus.—A second group of forms with union in the frontal body-plane includes those cases in which the fusion is dorsal instead of ventral, *i.e.*, back to back in place of front to front. Although theoretically the area of fusion may be at any point on the dorsal surface of the body it is almost invariably limited to the pelvic region. Living examples of this variety are shown in Figs. 118–120.

The internal anatomy of Pygopagi shows great variations. The free vertebral columns are always completely separate. In most cases there is a single sacrum and coccyx common to both components although occasionally, as in the case shown in Fig. 120, the skeletal connection is reduced to a ligamentous union only. In the majority of instances the larger vascular trunks of the pelvis inosculate freely. The digestive tubes unite in a single common rectum or anal canal. The genitalia—practically all described cases are females—may be separate but are usually partially united. The caudal ends of the spinal cords may be fused.

Pygopagi form a considerable proportion of human double monsters although they are not as numerous as the ventrally united forms. They are sometimes viable.

Forms United in the Horizontal Plane.—The varieties of double monsters which are united in the horizontal plane of the body are classed in two sub-groups: Those joined at the cranial pole, head to head (Craniopagus, Cephalopagus), and those joined at the caudal pole, pelvis to pelvis (Ischiopagus).

Craniopagus (Craniopagus, Metopagus, Cephalopagus, Acrocephalopagus).—In this extremely rare form of duplication the two components are united head to head in the parietal region, the vertical axes of the two parts being continuous. The external body form of one of these specimens is shown in Fig. 109. In the cases of this class of which descriptions are available, the epicranial soft parts and the calvaria are fused but the cerebra are independent. One of these cases apparently lived for several months after birth.

Ischiopagus.—An example of this form is shown in Fig. 110. The anterior surfaces of the bodies are united at the level of the umbilicus which is single. The legs are abducted to the right and left at right angles to the common pelvis and perineaii with genitalia are formed on the right and left sides of the body through the union of the left perineal region of one component and the right perineal region of the other. There is a single common anal opening on the posterior surface.

Ischiopagi, while very rare, are more frequent than Craniopagi.

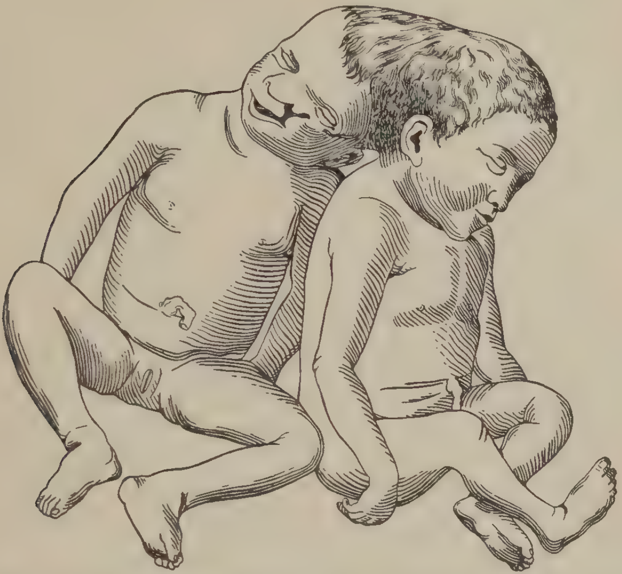

Fig. 109.—Craniopagus occipitalis. (From Schwalbe,[34], after Barkow.)

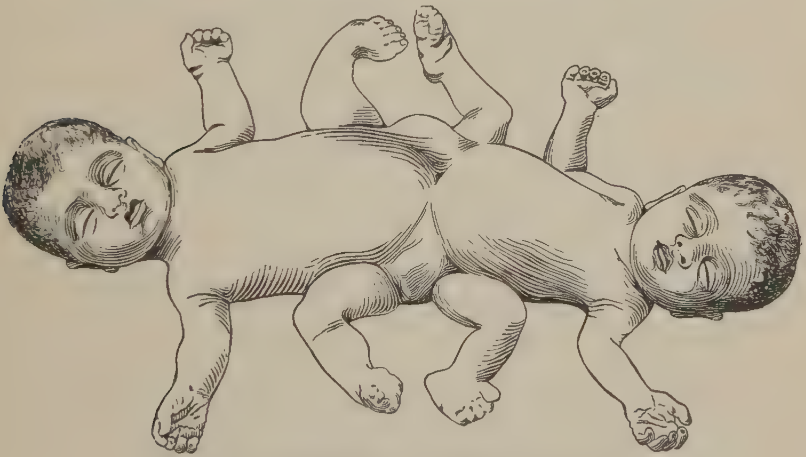

Fig. 110.—Ischiopagus. (After Baudouin,[3].)

Forms United in the Sagittal Plane (Duplicitas parallela).—This class includes three main sub-groups: Duplicitas anterior, Duplicitas media and Duplicitas posterior, and a fourth sub-group of combination and transition forms. All are comparatively rare in man but certain varieties are not unusual in some of the lower animals.

Duplicitas Anterior (Diprosopus, Dicephalus, Monosomia).—These forms have a single pair of legs and a single lower trunk while the upper part of the body is more or less completely duplicated. In the least marked cases the head alone shows some evidences of parallel duplicity as is indicated in Fig. 111. In others the cranial region is entirely doubled, the two heads being supported by separate necks from a common body. In still more marked cases the shoulders are also partially duplicated each bearing a pair of arms, or, as in Fig. 112, having three arms, the median one being common to both parts and formed from the elements of both components. In the most complete examples of this type of malformation the bodies are separate to the waist. Some of the more complete forms of Duplicitas anterior have lived for several months after birth.

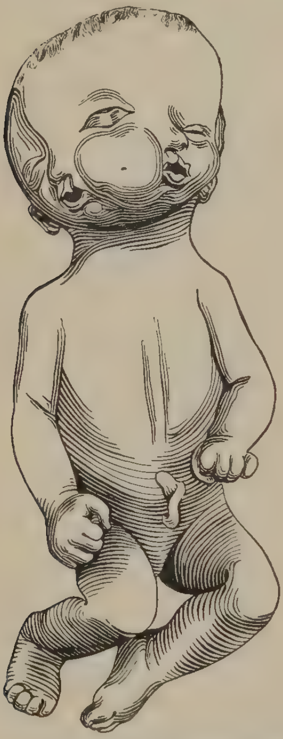

Fig. 111.—Duplicitas anterior (Diprosopus). (After Birnbaum,[6].)

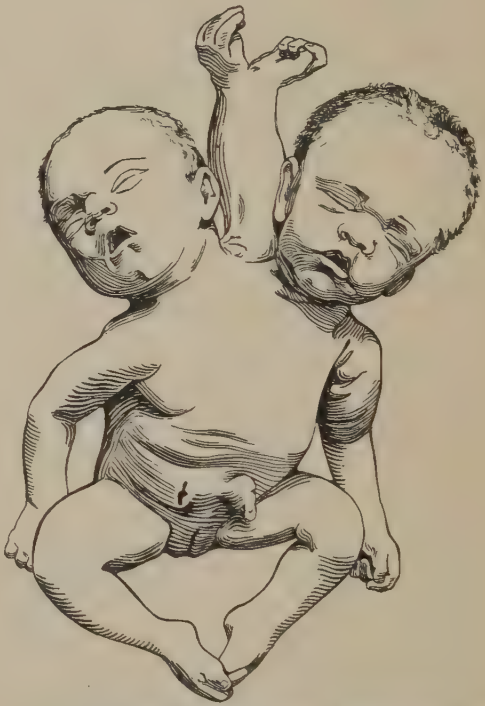

Fig. 112.—Duplicitas anterior (Dicephalus tribrachius). (After Stockard,[36].)

Duplicitas Media.—These are forms in which the body is single anteriorly and posteriorly but is duplicated in the middle region. Human examples of this variety have not been reported.

Duplicitas Posterior (Dipygus, Dilecanus).—In this group the parallel duplicity is confined to the caudal part of the body, particularly to the lower limbs and pelvis. Four legs with two perinei and two sets of genitalia are generally present. Often the medial pair of legs are reduced in size and sometimes they are fused into a single common limb which is usually deformed. The body is single above the pelvis and there is usually a single spinal column including a single sacrum. The digestive tube is usually single throughout. Some Dipygi are quite capable of extra-uterine life.

Combination Forms.—This category includes, in man, a few very rare cases in which both the caudal and the cranial parts of the body were partially duplicated and in which fusion in the sagittal plane was confined to the upper trunk and cervical region (Rachiopagus).

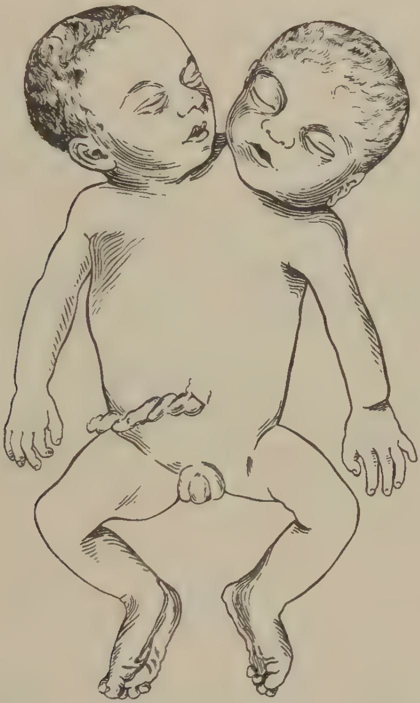

Fig. 113.—Duplicitas anterior (Dicephalus). (After Tribondeau,[40].)

ASYMMETRIC DOUBLE MONSTERS

The asymmetric double monsters include a large number of forms which differ greatly in external appearance and internal structure. The classification and limitations of the group are far from satisfactory. The distinction between certain highly organized examples and certain forms of symmetrical double monsters is mainly one of convenience, while, on the other hand, it is impossible to draw a sharp line between some of the less organized examples and certain teratomata. The asymmetric monsters are divided into several sub-groups on the basis of the position of the attachment of the less developed component (the parasite) to the more perfect one (the autosite).

Forms in Which the Parasite Is Attached to the Cephalic Regions of the Autosite (Craniopagus parasiticus, Janus Parasiticus, Epignathus and Related Varieties).—Craniopagus Parasiticus.—In these extremely rare cases, comparable to Craniopagus parietalis among the symmetric monsters, the parasite is represented by a head attached vertex to vertex to the head of the autosite. The best known example of this kind, which was described by Holm[19] over a century ago, lived about two years.

Janus Parasiticus.—Two or three recorded cases with partial duplication of the head in the frontal plane are classified under this heading.

Epignathus.—The Epignathi include a group of duplications in which the parasite is usually attached to the base of the skull of the autosite and projects through its mouth. Following Schwalbe, four sub-groups of parasites of the oral region may be recognized, namely: (1) Forms in which one more or less completely developed individual (the parasite) is connected with another by means of an umbilical cord which is attached to the palate of the autosite. (2) The parasite, which shows a certain degree of organization, is attached directly to the oral or palatine tissues of the autosite and projects from the mouth of the latter. (3) The parasite has the same position and attachments as in (2), but is an unorganized mass having the structure of a teratoma. (4) Small mixed tumors of the oral region. The forms usually termed Epignathi, which are rare, belong to the second and third categories.

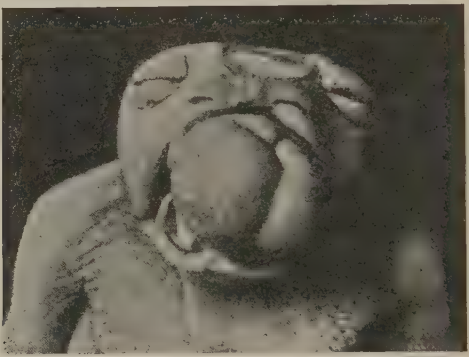

FIG. 114.—Epignathus. (After Schwalbe,[34].)

The more completely formed Epignathi generally consist of a rudimentary trunk with partially developed limbs. The less completely developed varieties, of which Fig. 114 is an example, generally show, on section, masses of connective, muscular, skeletal and glandular tissues and sometimes structures which can be recognized as ill-developed teeth, nodules of cerebral tissue and the like. Successful surgical removals of small Epignathi have been reported.

Forms in Which the Parasite Is Attached to the Ventral Surface of the Neck, Thorax or Abdomen of the Autosite (Thoracopagus Parasiticus, Epigastricus and Related Varieties). The majority of well developed examples of these forms may be compared to incomplete examples of Duplicitas anterior and posterior or with forms of frontal union of the symmetrical double monsters. An example of anterior duplicity is shown in Fig. 115, and of posterior duplicity in Fig. 116. A photograph of a living example of the latter variety is also shown in Fig. 125. Certain of these have lived for several years. There is at least one instance of a successful surgical removal of an Epigastricus.

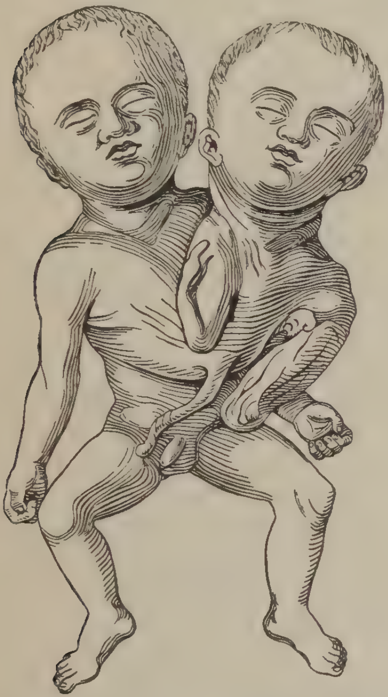

Fig. 115.—Supraumbilical parasite. Asymmetric duplication of the anterior half of the body. (After Schwalbe,[34], from Wirtensohn,[47].)

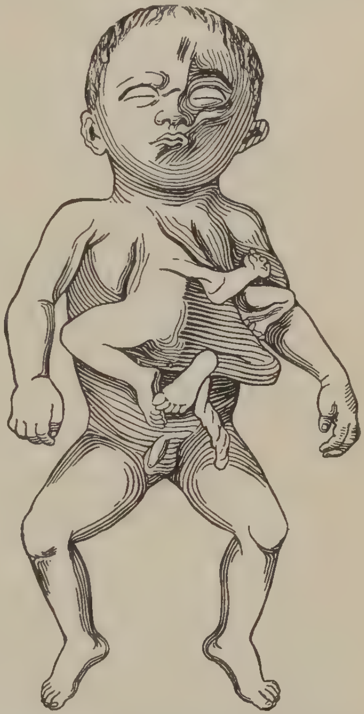

Fig. 116.—Supraumbilical parasite. Asymmetric duplication of the posterior half of the body. (After Schwalbe,[34], from Wirtensohn,[47].)

With these forms there should probably be included certain of the enclosed abdominal parasites and teratomata, some of which are highly differentiated.

Forms in Which the Parasite Is Attached to the Pelvis of the Autosite (Pygopagus Parasiticus, Pygomelus, Certain Sacral Tumors).—Again following Schwalbe, we may distinguish three main varieties of this group: (1) Pygopagus parasiticus and Pygomelus. In these forms the parasite is represented by a more or less malformed extremity attached to the sacral region of the Autosite. Sometimes these structures do not appear externally until after birth. (2) Sacral tumors in which the parasite lies in a cyst which is embedded in the pelvis tissues of the autosite. These may show a fairly high degree of differentiation. An example described by Moos,[24] is shown in Figs. 117, 118. (3) Certain, of the teratomata and mixed tumors of the sacral region may be included in the third and least differentiated class.

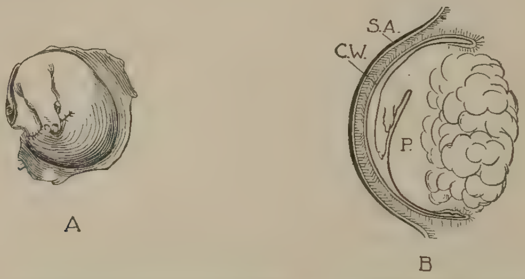

Fig. 117.—A subcutaneous sacral parasite. *A*, dissection of the specimen in its cyst. *B*, a semischematic cross section of the specimen. *P*, parasite with projecting limb; *S.A.*, skin of autosite; *C.W.*, lining of cyst containing the parasite. (After Moos,[24].)

FREQUENCY OF DOUBLE MONSTERS

Double monsters are so infrequent that the statistics on their occurrence are not particularly accurate. Mall[22] collated the statistics, of a number of observers and, on the basis of about 100,000 cases estimated that approximately 7 per cent. of all pregnancies terminated in aborted pathologic ova and about 0.6 per cent. in malformed children at term. Of the latter only a very small portion were conjoined twins. Puech,[32] examining a series of 100,000 births, found 517 malformations of various sorts. Of these only two (1:50,000 or 0.002 per cent. of all births) were double monsters. Even this small percentage is, in all probability, much higher than is usual. It is interesting to compare these figures with those of the frequency of duplicate or monozygotic twins, which are also forms of embryonic duplication, which has been estimated by Nichols[29] at about one-fourth of all twins or about two-tenths of 1 per cent. of all births.

More is known of the relative frequency of the various types of double monsters, Thoracopagi being by far the most common form in man. It is found, however, that both the total frequency of double monsters and the relative frequency of the several types vary greatly in different species of animals.

In the human species, female monsters are between two and three times as frequent as males. Curiously, monozygotic male twins seem to occur a little more frequently than females (approximately as 10 to 8.6).

THE VIABILITY AND POSTNATAL HISTORY OF DOUBLE MONSTERS

The great majority of double monsters are stillborn, generally before term. Certain forms, however, may survive for a variable period

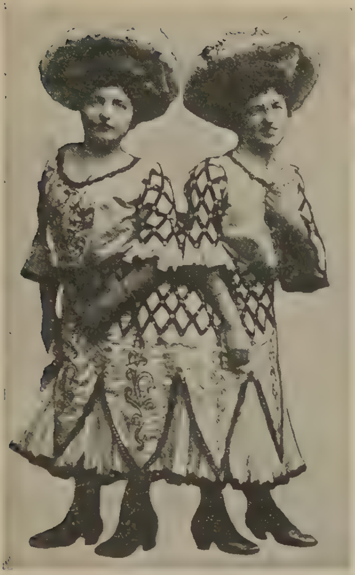

FIG. 118.—Living pygopagus twins, the "Bohemian Sisters." (After Bromann,[8].)

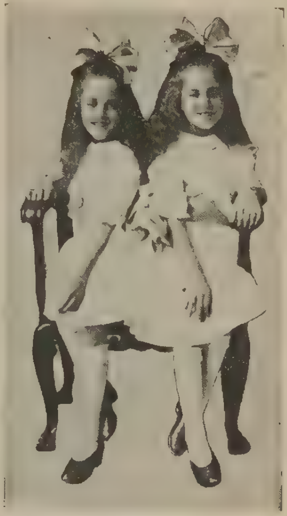

FIG. 119.—Living pygopagous twins about 12 years old, from an original photograph.

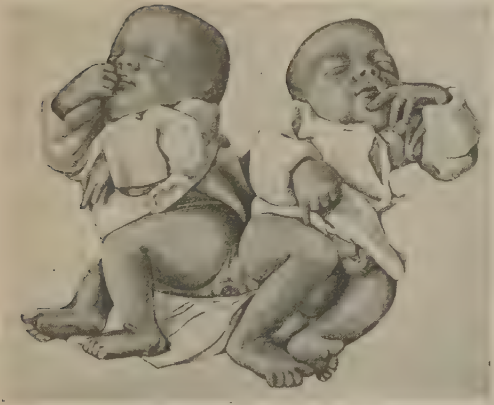

FIG. 120.—Living pygopagus twins, aged three months. (After Tynberg,[41].)

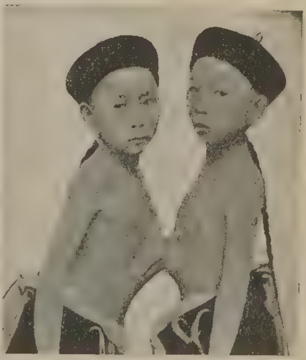

FIG. 121.—Living xiphopagus twins, the "Chen Brothers," about 15 years old. (After Baudóuin,[3].)

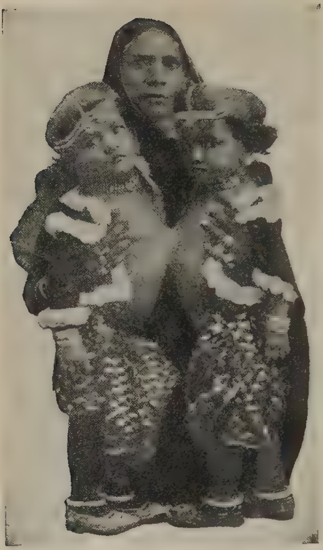

FIG. 122.—Living xiphopagous twins, "Radica-Doodica," about three years old. (After Baudouin,[3].)

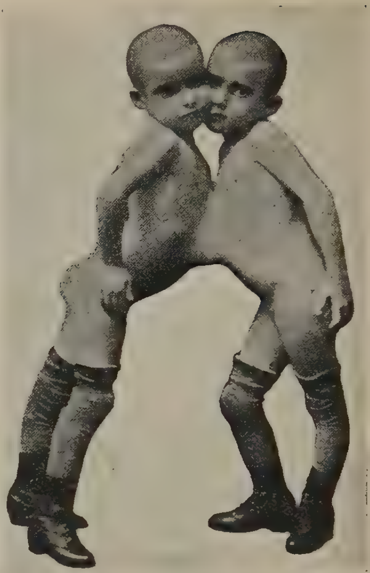

FIG. 123.—Living xiphopagous twins, "Maria-Rosalina," about 12 years old. (After Baudouin,[3].)

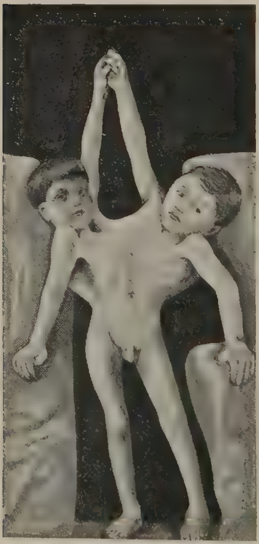

FIG. 124.—A living case of Duplicit as anterior, the "Tocci Brothers." (After Harris,[17].)

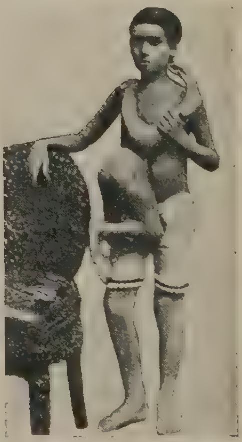

FIG. 125.—Living case of epigastricus. (After Bromann,[8].)

after birth and some may complete the full normal span of life. In general, the two classes of monsters most capable of post-natal life are, first, the symmetrical forms in which both components are of about equal size with a very much reduced connection; and second, those forms in which one component is very much reduced in size. The former class includes certain Thoracopagi, Sternopagi, Xiphopagi, and Pyopagi and a few cases of Duplicitas anterior. The latter includes some example of Duplicitas posterior and some asymmetric double monsters.

A considerable number of living double monsters ventrally joined in the frontal plane (Thoracopagi and related varieties, not including the Janus forms) have been reported. Although the majority of these cases have been children, the most famous example, the Siamese twins, reached the age of 63 years. Photographs of some of these are shown in Figs. 121–123. Descriptions of living Pygopagi are less numerous. Several of these have reached maturity, including the "Biddenden Maids," a well authenticated case living in the middle ages, who were 32 years old at the time of death; and the "Bohemian Sisters," whose pictures are shown in Fig. 118.

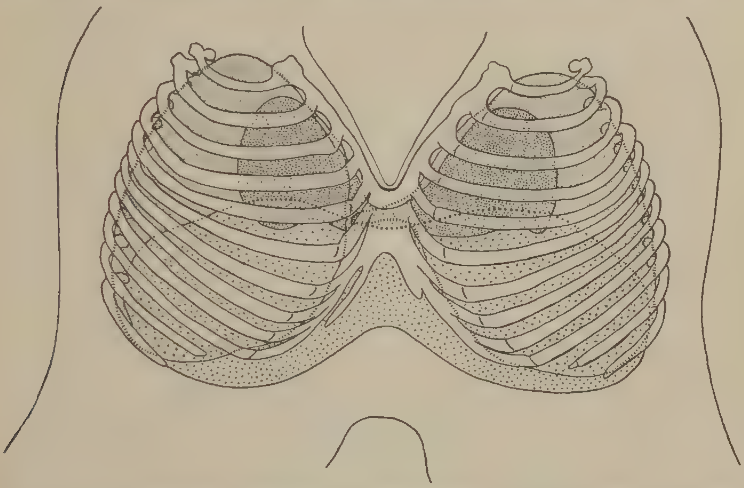

FIG. 126.—A diagram illustrating the relations of the thoracic skeleton, the pleural and pericardial cavities, and the liver in the xiphopagous twins shown in Fig. 123. (After Baudouin,[3]). Pleural cavities, light stipple; pericardial cavities, close heavy stipple; liver, spaced heavy stipple.

Among examples of Duplicitas anterior who survived for a considerable period are the "Tocci Brothers" shown in Fig. 124. There are several other cases of this kind. There are also several cases of living examples of Duplicitas posterior on record, perhaps the best known being that reported by Wells[45] in 1888. In these cases the duplicity is indicated only by a duplication of the lower limbs and a part of the pelvic organs.

Other types of symmetrical double monsters which have lived for brief periods after birth are noted in connection with preceding descriptions.

The components of lightly joined symmetrical duplications often show considerable physical, physiologic and mental differences. In particular, the rates of growth of the components may be quite different, even when both are in good health. This is brought out clearly by measurements and by the photographs shown in Figs. 119–123 inclusive. The pulse rates are generally different and not synchronous and the body temperatures may show some variation. There are several recorded cases in which one component suffered from an infectious disease and presented all the usual symptoms including elevation of temperature, while the other component remained unaffected. The death of double monsters generally follows the illness of one component, the exitus of the healthy twin occurring some minutes after that of the diseased one.

One of the best studies of living double monsters is that made on the "Chen brothers," shown in Fig. 121, by Vaschiede and Vurpas.[42, 43, 44] The following table gives a summary of their findings:

Observations on a Pair of Living Male Xiphopagous Twins (Liao-Toun-Chen and Liao-Sienne-Chen), Aged 15 Years

(Summarized from the data of Vaschiede and Vurpas)

	Liao-Toun-Chen	Liao-Sienne-Chen
Physical measurements:		
Height	1365.0 mm.	1350.0 mm.
Horizontal chest circumference	650.0 mm.	580.0 mm.
Maximum head circumference	505.0 mm.	510.0 mm.
Face height	108.0 mm.	106.0 mm.
Cephalic index	83.0 mm.	82.2 mm.
Physiologic measurements:		
Average pulse rate	92.0	80.0
Bloodpressure (radialartery, Potain sphygmometer)	14.0 cm. (SIC.)	15.0 cm. (SIC.)
Average respiratory rate	22.0	18.0
Vital capacity (Verdin spirometer)	1760.0 c.c.	1270.0 c.c.
Average muscular force (Régnier dynamometer)		
Right hand	24.5 kg.	17.5 kg.
Left hand	18.9 kg.	21.5 kg.
Axillary temperature	36.5°C.	37.3°C.
Mental measurements:		
Reaction time, auditory stimulus:		
Simple reactions, common stimulation	20.5	22.1
Simple reactions, separate stimulation	15.1	16.6
Reactions of choice, common stimulation	29.5	34.2
Simple reaction time, tactile stimulus:		
Common stimulation	19.0	14.7
Separate stimulation	17.3	20.2
Sensitivity to pressure (Verdin algometer)	100.0 gm.	60.0 gm.

THE SURGICAL SEPARATION OF SYMMETRICAL DOUBLE MONSTERS

The surgical separation of the various types of viable symmetrical double monsters has often been suggested and has been carried out in at least six instances. The first operation of this kind on record seems to be one described by König (1690). In spite of the time which has elapsed since this operation was performed the case is so well documented that it seems quite authentic. The subject was a female Xiphopagus, and the two components were connected by a slender, fleshy band just below the xiphoid process. The umbilical cord apparently arose from this structure at the time of birth. The connection consisted only of a sheath of skin enclosing a cartilaginous bar and a muscular and fibrous mass without large vessels or nerves. There was no communicating passage between the two peritoneal cavities. The operation was performed in infancy (exact age not stated) by means of a ligature which was placed around the connecting band and drawn tighter and tighter until the structure was greatly reduced in size when it was separated with a knife. Both twins lived, this being the only operation of the kind on record where both components survived more than a few hours.

In the second case (Boehm, 1860) the subject was a female Xiphopagus. The band of union between the two components began at the level of the xiphoid process and extended some distance caudally. This structure contained a cartilaginous extension from the xiphoid processes and gave rise to a single umbilical cord. There was no communication of the pericardial or peritoneal cavities and no connecting bridge of liver tissue. This case was operated at once. One twin died three days and a half after the operation, the other was alive and well five years thereafter.

In the third case (Biaudet and Bugnion, 1881) the subject was a Xiphopagus in which the connecting bridge contained a canal uniting the two peritoneal cavities, and a band of hepatic tissue between the two livers. The operation was performed three months old after birth. One twin died of shock six hours after the operation. The other died the next day with obvious symptoms of peritonitis.

The fourth case (Doyen, 1902) was the "Radica-Doodica sisters" shown in Fig. 122. One of the components developed active tuberculosis at about 12 years, and operation was advised to save the second twin. They were united in the lower thoracic and upper abdominal region by a band 12 to 14 cm. in height and about 5 cm. in thickness. This contained a cartilaginous bar from the xiphoid processes, a communicating channel between the two peritoneal cavities and a connecting pedicle of hepatic tissue which, on operation, was found to contain three large arteries. The operation was performed by Doyen in 1902. The sister more affected with tuberculosis died after several days of a tuberculous peritonitis. The other sister survived and improved.

A case of Xiphothoracopagus with more extensive union than the one described above was operated by Chapot-Prevost in 1902. This was the Maria-Rosalina case shown in Fig. 123. A semi-schematic drawing of the structures of the connecting band between the two components is shown in Fig. 126. The connection contained a cartilaginous bridge between the two xiphoid processes, connecting canals between the two pericardial peritoneal and pleural cavities and a considerable bridge of hepatic tissue about 8 cm. in diameter connecting the two livers. One twin died on the sixth day following the operation. The other survived.

In the last two cases described the greatest danger lay in the hemorrhage and shock incident to the division of the band of liver included in the band connecting the components. In the Maria-Rosalina case difficulty was also encountered on opening the canal which connected the two pleural cavities. Doyen recommends that in the future the operation of cases of this kind should be delayed until the age of 12 or 15 years unless called for by some emergency. This obviously does not apply to simple cases of Xiphopagi, such as the König case cited above, in which none of the serous cavities nor any part of the liver was involved in the connecting band.

Certain cases of very lightly connected Pygopagi appear possible of successful separation although apparently this has not been accomplished. In a case of Pygopagus described by Treyling in 1740 an attempt was made to separate the twins with caustics which resulted in the death of both. It is stated in the original description of the Pygopagus shown in Fig. 120 that the twins would be separated surgically at a later time but I have been unable to find any account of this being done.

A detailed consideration of the surgical separation of conjoined twins will be found in the monograph of Baudoin[4] from which much of the material in this section is derived.

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CHAPTER CLXV

VULVOVAGINITIS

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Vulvovaginitis is a chronic inflammatory disease of the lower genital tract in girls. The term vulvovaginitis is hardly adequate. As will be shown, the urethra and cervix are frequently involved and other genital structures occasionally. Though mild in its manifestations the condition should not be neglected nor treated lightly as it is highly communicable, and may be a source of blindness in the patient or her attendants. In children the disease is essentially different from that which occurs in adults. Complications frequently occur in adults whereas in children they are rare. Serious complications occasionally occur and may even prove fatal.

Etiology.—The period of greatest frequency in childhood has been stated by Pott as the first five years of life. The infection may occur at any age up to puberty. Birth infections—vulvovaginitis neonatorum—are not as frequent as ophthalmia, but have been reported by Epstein and others. Birth infection is said to occur more frequently in breech presentation, communicated from the birth canal of gonorrheal mothers. Direct contact due to sex violence, and in cases of precocious sex indulgence in older children constitutes a small proportion of cases. By far the commonest mode of infection is by *indirect contact.* Under this heading there are numerous sources of transmission. In sporadic cases seen in office or dispensary practice, some adult member of the household is usually responsible, the child being contaminated by bed linen, wash cloths, towels, and other articles. The joint occupancy of one bed by the child and an infected person is held to be a common source of contamination. In hospitals, where epidemics are common, nurses' hands, thermometers, bedpans, enema points, catheters, bath tubs, toilet seats, wash cloths, towels, and napkins are sometimes responsible. Flies are considered by Welde as a possible source. Epidemics are of frequent occurrence in childrens' hospitals, asylums, and girls' schools. A single admission of an infected patient to an institution may be the source of a virulent epidemic. Even the public bath has been ascribed as a source of epidemic, as in the classic instance described by Skutsch, wherein 236 girls were infected with gonorrhea. It is noteworthy that no boys using the bath were infected. Boys are not subject to genital infection in the same degree as girls. Only rarely does urethritis occur in male babies. Rectal infection in male infants must not be overlooked, for as Byfield and Floyd recently reported, its presence may endanger female babies occupying the same ward. In this instance six male infants occupied a ward where there was an epidemic of vulvovaginitis. The girls were removed to the isolation hospital and the boys transferred to another ward. A girl baby who was admitted to the boys' ward developed a specific gonorrheal discharge four days later. Smears from the rectal mucosa of the boys were positive. The rectal thermometer was considered by the authors as the most likely agent in the transmission of the infection. The various sources of infection in vulvovaginitis and their relative frequency were well summarized by Fife, Gittings and Carpenter from answers to a questionnaire sent to a number of social agencies:

Infection in some other member of family	102
Hospital wards	107
Hospital dispensaries	1
Playmates	31
Sleeping arrangements	14
Toilet and bathing facilities	10
Public schools	8
Temporary institutions (boarding homes)	13
Permanent institutions	1
Day nurseries	5
Bad habits and bad character (probably in older children)	15
Rape	8
Doubtful	93

The direct exciting cause of genital tract infection is bacterial invasion. The disorder produced by the gonococcus of Neisser is the most serious. Pearce differentiated two more or less distinct types of gonococcus by agglutination and complement fixation tests—the infant and the adult varieties. These types corresponded to the clinical course of the strain whether from the acute urethritis in the adult or from the vulvovaginitis of infancy and early childhood. The distinction between the two types, according to Pearce is not an absolute one. It is highly significant that in no instance did any agglutination of either type of gonococcus occur with sera immune to diplococcus intracellularis or to micrococcus catarrhalis. It was also noted that no complement fixation occurred with meningococcus antigen and gonococcus immune serum, nor did any occur with gonococcus antigen with either meningococcus or catarrhalis immune serum.

The percentage of cases in which the gonococcus is present varies considerably. It is obvious that during an epidemic the specific organism is present in almost every instance. This applies equally if the epidemic occurs in private practice or in a childrens' asylum. In the protracted cases the gonococcus is frequently not found even in specific cases. In dispensary practice the non-specific organisms are more often encountered, due to faulty hygiene. Abt believes that the gonococcus is causative in 70 to 80 per cent. of infected children. Hurdon reported 63 per cent. gonorrheal from the Johns Hopkins

Dispensary, and Spaulding found 65 cases of gonorrhea among 83 cases of vulvovaginitis. In 42 children studied culturally at the Michael Reese Dispensary, Chicago, 35.7 per cent. were proven to be gonorrheal and 64.3 per cent. were due to non-specific organisms (Anderson, Schultz and Stein). Their bacteriologic investigations revealed a group of organisms which seemed to be derived chiefly from the intestinal tract. Staphylococci and Streptococci, chromogenic Gram-negative cocci, Gram-negative bacilli of the B. Coli group, and Gram-positive diphtheroids were isolated in cultures. Filth and general unhygienic surroundings doubtless predispose to the infection. In some instances, uncleanliness appears to be the sole cause, for attention to personal hygiene clears up some of the non-specific, non-virulent cases.

Bad habits such as masturbation, and the introduction of foreign bodies into the vagina are more frequently responsible in mentally deficient children. The exanthemata definitely predispose to genital tract infection in girls. Some children contract vulvovaginitis for the first time during an attack of an exanthematous disease. In others a latent infection becomes manifest during an acute eruptive disease. Spaulding mentioned a non-specific variety of vulvovaginitis following chickenpox and measles due to Staphylococcus and Streptococcus. Stein reported a case of gonorrheal infection following chickenpox and another after measles, both of whom were kept under observation to note the effect of treatment.

Pathology.—Although Scholtz asserted that the cervix in children is immune from vaginal infection, Rubin and Leopold, Norris and Mickelberg, and in fact practically all observers who have employed an endoscope or vaginoscope in the study of vulvovaginitis claim that the vaginal portion of the cervix is a constant seat of infection. Sometimes the cervical canal is involved, and a purulent cervical discharge and even ectropion of the cervix were reported. At post-mortem examination Hess observed a frequent involvement of the cervix in these patients. The uterine cavity, tubes and ovaries are rarely invaded. The urethra is regularly involved in the gonorrheal cases, and Bartholin's ducts and Skene's glands more commonly infected than is usually admitted, but not so commonly as in the adult. According to Norris and Mickelberg only the outer portion of Bartholin's ducts are involved due to their small caliber and the fact that the glands do not functionate so actively in childhood. The involvement is bilateral when it does occur (Welde). Vaginitis is a constant lesion. The mucosa is a dull pink with occasional hemorrhagic spots and pus on the rugæ. The vulva, labia and vestibule may be bright red and covered with yellow-green pus, with some crusting at the edges. Inguinal glands may be swollen. Bladder involvement is rare. The rectal mucosa is frequently infected, the mucosa appearing red, but without swelling or ulceration.

Symptomatology.—Noeggerath and Eckstein present the following clinical classification of vulvovaginitis.

I. *Gonorrheal vulvovaginitis.*
II. *Non-gonorrheal vulvovaginitis.*
  1. Exudative diathesis.
  2. Desquamative catarrh of newborn (physiologic).
  3. Non-specific infection—colon bacillus, staphylococci, catarrhal states in measles, variola, varicella, and scarlatina. The clinical course may resemble the specific type and tend to persist obstinately.
  4. Aphthous vaginitis (Heubner).
  5. Diphtheritic vaginitis. Rare (Lande, Kobrak).
  6. Vaginitis masturbatoria. Redness and swelling of labia and introitus. May be complicated by foreign bodies in older children with purulent discharge.

There can be no doubt that genital infections in infants and girls may be due to gonococci or other organisms and in any instance may be extremely contagious. Epidemics of gonorrheal and non-specific varieties have been carefully studied (Baer). Not only is the vaginal mucosa in small girls extremely susceptible, but it is less protected than in the adult. This may be explained by the absence of hair and the eversion of the vulva.

The incubation period of vaginitis is usually three or four days, and subjective symptoms may be entirely absent. Yellowish, stiff spots on the linen often first attract attention to the condition. The desire to urinate may be increased, and if the skin of the vulva is irritated, there may be burning upon urination, or pain when walking. Pus may be observed by the mother or nurse and a larger amount can usually be pressed out of the vagina by inserting a finger into the rectum. (Danger of transmitting infection to the rectal mucosa must be borne in mind.) While purulent discharge is the outstanding sign of the disease, sometimes no purulent secretion is observed and the diagnosis can be made only by bacteriologic examination. This is particularly true in latent or chronic cases. In the acute stage there may be an elevation of body temperature, and itching and burning sensations about the vulva may be present. The course of vulvovaginitis is generally chronic. Various writers maintain that the disease lasts from six days to six years. The average course is probably from three to six months. Mild non-specific cases are of shorter duration where the hygienic conditions of the child are improved.

Complications.—The extreme rarity of complications is considered as a strong argument for the view that vulvovaginitis is *never* gonorrheal. Cultural and serologic studies (Pearce, Rubin, Stein) have established beyond all doubt the specific nature of gonorrheal infection in vulvovaginitis. Furthermore, nurses have suffered from gonorrheal ophthalmia during a hospital epidemic (Fife, Gittings and Carpenter). On the other hand vaginitis has been observed secondary to ophthalmia. This is of rare occurrence. According to Kaumheimer it is believed that the child acquires an immunity in other mucous membranes to its own gonococcus. Dermatitis, inguinal adenitis and arthritis are the most commonly reported complications. Welde observed that the joint affections assumed the form of a polyarthritis which usually terminated fatally. Less frequently, cystitis, salpingitis, pelvic or general peritonitis, endocarditis, sepsis, ophthalmia, proctitis and Bartholinitis have been observed. Among the late sequellæ are noted endometritis, gynatresia, sterility and dysmenorrhea.

Diagnosis.—The diagnosis of vulvovaginitis is frequently made by inspection. Redness of the vulva and a vaginal discharge are observed. For recognition of the type of infection, smears must be carefully examined, preferably by an expert bacteriologist. Diagnostic errors have been frequent due to carelessly prepared smears, poorly stained, and incorrectly diagnosed. Smears should be made upon clean glass slides with a wire loop, a pipet, or sterile cotton swab. Kolmer advised that the latter be dipped into weak bichloride solution, moved about in the vagina and then rolled, not rubbed over the slide. Rubin concluded from his study of 255 cases that too much value is placed upon smear examination, and that the accurate diagnosis rests upon cultural and serologic tests. Smith first described a complement fixation test for gonorrhea in 1913, and considered it a specific reaction. Kolmer obtained only 50 per cent. positive results with it, and Irons and Nicoll believe it has limited value. Gonococcus cultures were obtained in only 50 per cent. of the cases in which positive smears were found in Stein's series and he concluded that cultures are not requisite for diagnosis. Norris, Noeggarath, and others agree that the finding of gonococci in the smear is diagnostic. A positive diagnosis of gonorrhea may be accepted if upon smear examination the following are found: pus cells with Gram-negative intracellular diplococci with typical morphologic characteristics of the gonococcus.

It may be necessary to examine repeated smears, and provocative injections of silver nitrate solutions into the vagina, or parenteral injections of foreign protein may disclose a specific infection where otherwise negative results are obtained. The latter procedure becomes valuable in chronic cases which may have been treated previously and in which organisms are scarce in the smear.

Prognosis.—While vulvovaginitis is in itself not a fatal disease, it may when complicated be very serious and deaths have been reported from gonorrheal arthritis, peritonitis, sepsis and endocarditis.

The tendency to latency and recurrence must be emphasized, and therefore a long period of observation is necessary to establish permanency of cure. Welde says six months must elapse with repeated negative smears before a cure is definitely established. Dorne and Stein advise a period of observation with bi-weekly negative smears, for as many weeks as were required to cause disappearance of symptoms. J. Muller examined his patients every two weeks for one year and every three months the second year for detection of recurrence.

In asylum children and those kept in hospital wards the course is apt to be chronic, due to low resistance, and possibly to repeated inoculation. In children of well conducted homes, the prognosis is better.

Treatment.—Bearing in mind the extreme contagious character of the infection and the sources of indirect contact which may be responsible for its spread, a strict prophylaxis must be enforced in all admissions in childrens' homes, hospitals and asylums. The recognition of the fact that many children are latent carriers demands routine admission smears and isolation for a definite period of observation until all suspicion can be eliminated. At least three negative smears on consecutive days should be obtained before girls should be admitted to general wards. Cases of vaginitis arising in a ward should be removed immediately and either isolated or discharged. To prevent birth infection, Epstein recommended that female babies born of gonorrheal mothers have the regular Credé treatment applied to the vulva and that potassium permanganate be added to the water of the first bath.

Children should always sleep alone and should be taught how to properly cleanse themselves. Frequent inspection of the genitalia by the mother or nurse is urged and cleanliness insisted upon. Gonorrheal children must be kept from school. In those who are suffering from the non-specific form, the infection is usually due to the colon bacillus or some other organism derived from the intestinal tract. Such children need not be excluded from school attendance Special U-shaped toilet seats are recommended for institutions, and school authorities should be urged to have the toilet seats kept clean.

Children in all institutions should have individual beds, thermometers, bedpans, soap, towels, washcloths, and other necessary utensils. Nurses must learn to practice the strictest aseptic technique in handling children. The danger of an infected nurse or nurse-maid must also be borne in mind. The use of rubber gloves by nurses in handling suspicious cases is to be commended.

In the active management of vulvovaginitis unquestionably rest and cleanliness are important factors; daily tub baths and the use of clean under-garments should constitute a part of the routine treatment. The intravaginal use of antiseptic irrigations and suppositories, of Bulgarian bacilli, of Bolus alba, of yeast, the resort to thermal baths, of serum injections and intravenous therapy, must all be looked upon with skepticism because of their ineffectiveness or the possible occurrence of complications.

Vaccin therapy was at one time recommended as a highly successful method of treatment, Hamilton, Butler, Wolff and others reporting as high as 75 to 90 per cent. cures. Failures in the hands of Barnett, Wollstein, Noeggerath and others serve to detract from its value. Complicating arthritis, however, was said to be benefitted by vaccin therapy (Barnett). Abt is of the opinion that vaccins are valueless in vulvovaginitis. More recently J. Muller has revived the interest in this form of therapy in the use of Gonargin. His first report appeared after an observation period of eight months, when 21 out of 28 cases of gonorrheal infection had remained free from recurrence. He again reported on the series at the end of two years, with five additional cases cured and no recurrences in any of the series. Muller believes that results are better in old chronic cases which have received other treatment, and are less favorable in acute cases. Kruspe utilized Muller's method in 15 cases of gonorrhea in girls, six with chronic, and nine with acute infection. After using Gonargin from three to four months, *only one case was cured*, nine were not improved, and five which apparently had improved suffered recurrences three to four weeks after treatment was terminated. In the present state of our knowledge of vaccins, no great enthusiasm can be shown for this type of therapy, particularly where it is utilized as the sole mode of procedure. When both local antiseptics and vaccins are used, one is left in doubt as to the relative value of each agent, and the results are no better than with local treatment alone. Under the latter caption, two significant methods of treatment have been developed in the past three years which bid fair to replace practically all the older methods.

1. Norris and Mickelberg have described in detail the use of Dakin's solution which resulted in cure of gonorrhea in an average of 12 weeks, and of 63 cases analyzed, only eight (12 per cent.) recurred. They first utilized the method described by Wachs and Mazer of a daily instillation into the vagina of 1 per cent. Dakin's solution in olive oil with the children in knee-chest or Trendelenburg posture, and later examined them with the electrically lighted urethroscope to detect unhealed areas on the cervix or vagina. Such areas, as well as the cervix and urethra were treated in the end stages of the infection with mercurochrome. In refractory cases they dried the vaginal mucosa thoroughly with hot air after which 1 or 2 per cent. mercurochrome solution was applied. This drying treatment was carried out three times a week, the object being to develop a more resistant vaginal mucosa. An observation period of three months after the conclusion of the active treatment is advised by them before declaring a cure.

2. The use of an ointment vehicle for antiseptic treatment of vulvovaginitis has been extensively employed with considerable success. Gellhorn in 1920 recommended the use of 1 per cent. silver nitrate incorporated in an ointment of equal parts of lanolin and vaselin in vulvovaginitis. He observed a rapid disappearance of the vulvitis and the discharge. Following this principle, Stein used mercurochrome-220 soluble, similarly in a 1 per cent. ointment, and reported his results with the daily injection into the vagina of this preparation in 59 patients, 30 per cent. of whom were gonorrheal. Subsequently Dorne and Stein supplemented this with a second report bringing the total number treated to 73, with the following results:

18 Gonorrheal patients cured in an average of 9.7 weeks.

15 Suspicious gonorrheal (old chronic cases) cured in an average of 6.5 weeks.

40 Non-gonorrheal (culturally, organisms from the intestinal tract) cured in 5 weeks.

Twenty of the patients were kept under observation for one year after the conclusion of the treatment and were found to have remained free from recurrence.

The use of mercurochrome ointment has many advantages. First, it is preferable to the instillation of fluids as it holds the medication in contact with the diseased mucosa continuously and penetrates deeply into the folds of the vagina. Second, it is a simple and painless method. Third, mercurochrome is less irritating than silver nitrate, is less astringent, and is equally germicidal. As seen from the above results, it is rapidly effective in non-specific infections, and very much more effective in the specific cases than any other gonococcide hitherto employed.

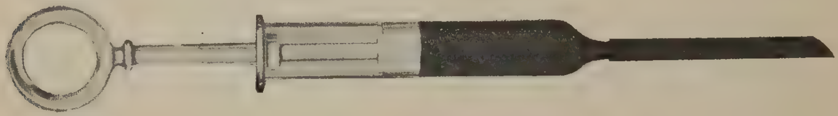

Fig. 127.—Mercurochrome ointment in syringe ready for treatment of vulvovaginitis. Ointment composed of equal parts of lanolin and vaseline containing 1 per cent. "Mercurochrome—220 Soluble" (H. W. & D.). The mercurochrome must be dissolved in a minute quantity of water, before incorporating with ointment base. The ointment should be warmed in a water-bath to facilitate drawing it into syringe.

The ointment is injected into the vagina by means of an ordinary glass irrigating syringe having a slender nozzle (Fig. 127) to which a piece of sterile soft-rubber tubing 3 in. long and ¼ in. in diameter is attached. This tubing is introduced into the vagina without injury to the hymen and is slowly pushed inward along the entire length of the vagina. The vagina is then slowly filled to capacity with the mercurochrome ointment, the exuded ointment serves as a protecting medium to the irritated vulva. A vulva pad prevents staining of the clothing by the drug. The tubing is changed for each patient and is sterilized by boiling. These treatments are given daily and no irrigations or other intravaginal treatments are permitted, but a daily tub bath is insisted upon. The mothers are urged to change the children's underclothing frequently. The method is so simple that a large number of children may be treated in clinic in a short time; it is painless, so children learn to coöperate readily. In some instances injections given two or three times a week were effective in diminishing discharge and alleviating symptoms and there was always evidence of the drug in the secretions when a day or two had passed since the treatment was given. Smears and cultures were taken by Stein at the beginning of treatment, and repeated every two weeks after a day of rest from treatment. When negative reports were obtained this procedure was repeated at weekly intervals until three successive negative smears and cultures were obtained. Treatment was then suspended, smears and cultures were then taken two weeks later and if negative repeated finally in three or four weeks to determine cure.

Further observation was continued for a period equal to the time of the active treatment before the patient was discharged as cured. Furthermore, these patients were kept under observation for a year to determine the permanency of the cure and to detect recurrences. All who could be continuously observed (20 children) remained free from infection. The advice of Rubin and Leopold, Norris and Mickelberg and others to utilize the electrically lighted vaginoscope for final inspection of these children before discharge is sound and reasonable. Small unhealed areas may thus be detected, and topical applications of silver nitrate or mercurochrome may be made and a cure thus insured where otherwise recurrence might ensue. The use of provocative injections of silver nitrate, or of parenteral protein injections may also be employed in the determination of cure.

Vulvitis.—In addition to gonorrheal vulvitis and that occurring in the non-specific infections mentioned above, more rarely other organisms may produce inflammation of the vulva. The bacillus Diphtheriæ may produce extensive membranous and even ulcerative vulvitis which may cause great tissue destruction. Bacillus Typhosis and Bacillus Dysenteriæ have been known to cause ulcerative lesions of the vulva. Similar inflammatory lesions have sometimes been observed following scarlet fever, measles, variola, and cholera. A primary vulvitis due to the Pneumococcus has been described which preceded the occurrence of pneumonia by several days. Vaccinia of the vulva was reported by Benneke in a girl eleven years old.

Tuberculous lesions of the vulva are rare. When they do occur they appear as ulcers. Raymond and Hamburger reported two instances of primary vulvar tuberculosis, although such lesions are usually secondary. Syphilitic vulvitis is also rare. Diffuse infiltration of the outer border of the labia majora and of the genito-crural folds has been described in lues.

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CHAPTER CLXVI

ARTHRITIS DEFORMANS

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History.—Arthritis deformans, one of the most distressing afflictions of childhood seems to be becoming more common as the years go on. Known to the ancients in the adult form, in Rome[1] and Egypt,[2] it did not seem to spare the primitive Germanic tribes which might have been expected to lead a more hygienic form of existence. Those Germans living along the shores of the Baltic Sea and the Egyptians who had their homes on the banks of the river Nile seemed to be more prone to the disease. In modern times we are accustomed to associate the disease in adults with England; for it is from that country that the earliest and most frequent medical reports have come. The disease occurs chiefly in sporadic form, although Beek[3] states that there is a region of Siberia where as many as 46 per cent. of the children, between the ages of 8 and 13 years, are said to have a chronic osteoarthritis.

Early medical writings are silent as far as mention of a possible juvenile form is concerned. Neither Felix Wurtz[4] nor Meissner[5] who gives the pediatric bibliography previous to the year 1850 speak of anything, even remotely suggesting the disease. Cornile[6] in 1864, and after him Charcot[7] in 1866, are usually stated to have been the first to mention chronic deforming arthritis as seen by them in childhood. The first more exhaustive article is that of Moncorvo[8] who likewise can find no significant earlier writing on the subject. He quotes Niemeyer (1869) who stated that children possessed an absolute immunity to nodular rheumatism, one of the terms applied to the affection under discussion. In this country Smith[9] referred to a case seen by him in 1871, as "one of great rarity." Von Wahl[10] in "Gerhardt's Handbuch" also bespoke the extreme infrequency of the disease seen only following acute post-infectious polyarthritis. As late as 1882,[11] Lacaze-Dori was able to gather but 12 cases from the literature.

The series of cases of Diamantberger[12] did not appear until 1891, and the famous communication of Still[13] in 1897. Since that time there has been no great lack of writings, and it is possible to find clinical data of several hundred cases. Arthritis deformans of childhood is no longer a rare disease.

Terminology.—A word as to nomenclature may not be out of place in view of the confusion which existed more in the past perhaps than at present. The name "rheumatisme noueux" was early used by Charcot. Then someone added the adjective "deformante" as more descriptive, so that this term or its Latin translation "rheumatismus nodosus" with or without the modifying "deformans" was in common use. The English writers have preferred to employ either "rheumatoid arthritis" and, less often, the simpler "arthritis deformans." Benign hyperplastic synovitis of the German writers never enjoyed much vogue and may well be forgotten in that it emphasizes but one of the pathologic changes encountered and that probably not the most important. Schueller[14] has spoken of a polyarthritis chronica villosa (chiefly adults) with the intention of again emphasizing what seems to him a greater or lesser involvement of the synovial membranes. The "rheumatisme fibreux" of Jaccoud[15] is applied by him to a special "dry" form. Still in his well-known paper avoided any specific designation, preferring to the names in common use, the title "On a Form of a Chronic Joint Disease." Since that time it has grown to be the custom to refer to the deforming arthritis of childhood as Still's disease.

There are two reasons why this is not appropriate. In the first place, the disease was known before his report. Then, it seems probable that the symptom-complex that he so excellently described is no more than a stage or a degree of severity of the affection itself, for it is clear from the literature that there are many cases of chronic joint disease in which the involvement of the spleen and lymph glands is absent or slight. It would not be out of place, however, to speak of "Still's variety" or form. The objection that might be raised to the use of the term arthritis deformans is that the disease process is so largely outside of the joint. When all is said and done, however, there is probably no better name than arthritis deformans, as it is sanctioned by long usage, descriptive in a general way of the disease, and of its probable etiology and expected pathology. It is no more necessary to use the modifying "juvenile" than it would be in the case of diabetes or scurvy, and, certainly anything which would tend to stress the question of the identity or difference between the disease in childhood and its manifestations in adult life or in senility would only tend to overemphasize one phase of a condition now none too well understood.

Pathology.—In spite of the fact that arthritis deformans of itself so rarely leads to an early death, and even though there have been few pathologic studies made of the disease in childhood, enough is known, thanks to the fact that it has been possible to produce identical changes experimentally in animals, to permit a fairly satisfactory picture to be drawn.

Our clinical experience should lead us to suspect that in the early stages of the disease in childhood, the joint cavity and the cartilages are relatively free of damage.[13, 16, 17, 18, 19] This is actually the case. The chief primary changes are most frequently in the joint capsule itself, while the lateral synovial membrane is later involved. In these tissues there is found a greater or lesser degree of serous or sero-fibrinous exudation together with cellular infiltration, if we accept as characteristic the biopsies of Spitzy[20] and the results of those who have produced the comparable changes by bacterial inoculation.[18, 21] The lateral involvement extends well on to the attachments of tendon and often includes the bursæ. This sero-fibrinous exudation is a most important part of the disease since it is not completely absorbed but tends almost invariably to become organized with connective tissue which later contracts to form a fibrous scar-like sleeve.[18, 20] This is the cause of a large part of the disability seen in the early period.

Synovial changes of somewhat the same character are found; but owing to the nature and location of this tissue, proliferation rather than contracture seems to be the nature of its first reaction. Whether marked increase of villa formation is the rule is not established. Later in the disease contracture of the synovia may also take place. In those joints where there are intercartilaginous ligaments there is said to occur an increase of fat tissue.

The formation of varying amounts of intra-articular granulation (the so-called pannus) due to proliferative changes in the perichondrium occurs probably in response to the stimulation from destruction of joint cartilage or subchondral tissues.

All observers[17, 22, 23] are agreed that the changes which have been produced in the joint cartilage are not to be seen early. They may be secondary to the subchrondral irritation produced by the causal factors of arthritis deformans; and they are most probably exaggerated by such static disturbances as arise from the joint dysfunction (pressure and faulty apposition) and are, in part also, the result of reparative proliferation. The cartilage changes vary from subtle loss of normal nutritive state with significant alteration of architecture (fibrillation) to actual destruction. There may be observed anything from a loss of smoothness and gloss to pitting or actual erosion. The repair is through the medium of a proliferated perichondral membrane, which is said to possess the power of transforming itself into bone or cartilage.

The subchondral changes are of a complex nature and vary greatly at different stages of the disease and may differ in the same bone at the same stage. In general, they may be summed up as being a destruction of cartilage and bone with reparation through fibrous tissue formation and new growth in atypical arrangement of cartilage and bone. There results an irregularity of the line of provisional calcification which bears a superficial resemblance to that seen in rickets, but here the resemblance ends, for there is no comparable degree of decalcification. The end results of these more deep-seated epiphyseal changes, which are seen only in the later stages of this disease, are due to a permanent alteration of the architecture of the joint—one which precludes anything like a restoration of normal function. Such terminal gross changes, as either dislocation or fibrous or even bony ankylosis, are not infrequent. These may occur in combination. Osteophytes or Heberden nodes are rarely seen in childhood.

A word or two as to blood-vessel changes may not be out of place in view of the rôle these may play in the maintenance of the pathologic processes. There is first of all in the involved tissues a proliferation of capillaries; this is later negatived by connective tissue formation which in its contracture obliterates them; and there may also be obliteration from within. The effect of this on nutrition of the affected parts is obvious.

Bacteria have been found by some[20, 24] but have been missed by most observers. This holds true also in the disease experimentally produced.

Etiology.—Early writers have little to say as to the direct primary causes, reflecting thereby the lack of definite knowledge of the exciting causes in adults. At this time, also, there had been so few cases of the juvenile form of the disease encountered, that the question of the relationship had been little more than discussed. There were, however, enough similarities to warrant the carrying over of the current theories of causation, namely, that the affection was either of metabolic or of nervous origin.

At the time that the metabolic theory of arthritis was prevailing there were no reliable or extensive biochemical studies made which would now be regarded as lending support to this view. Birk[25] could find no abnormality of calcium, magnesium, phosphorus or nitrogen metabolism in a severe case in which *x*-ray pictures suggested that a decalcification process was going on.

All subsequent studies of a physiologic and biochemical nature worthy of mention, have been carried out in adults. The latest[26] of these has revealed such subtle changes as lowering of the sugar tolerance, rise in oxygen saturation of the blood, slight lowering of the basal metabolic rate, and variation of the blood flow with considerable slowing, but the exact part that these changes play in the morbid processes has not been demonstrated. As a matter of fact, Pemberton[27] in his latest resumé of his work admits that he now has a new "slant" on the subject and feels that while a betterment of the sugar tolerance may be observed with improvement in the arthritic process, still the faulty chemistry fails to throw much light on the mechanism of the disease itself. He admits that "even though there is a fundamental dislocation of physiology" that a large number of cases of chronic arthritis is caused by some form of infection.

Mitchell in 1831,[28] and Remak in 1863,[28] were among the first to entertain the possibility that such extra-articular manifestations, such as sweating, glossiness of the skin, trophic changes in the nails, the disproportionate wasting of the muscles with spasticity, seemingly greater than could be expected to follow disuse, appearing as it sometimes did before the joint disability had existed for any considerable time, were due to an involvement of the nervous system. These with the symmetrical involvement of the joints led Charcot and others to hold to a nervous origin of chronic deforming arthritis (in adults). Further support of the nervous origin of the disease was seen in the occurrence of joint changes in certain cases of tabes and syringomyelia.

As a matter of fact, post-mortem studies revealed quite definite pathologic changes in sensory nerves, posterior nerve roots, and in the dorsal columns of the spinal cord. While it is true that others have not been able to confirm these findings in part or in their entirety the recent experimental work of Nathan[29] has done much to reconcile these conflicting results. He found that following the injection of hemolytic streptococci there developed a varying amount of epidural exudation with distinct venous congestion. An extension of this sterile inflammatory reaction to the adjacent intervertebral notches led to irritation and pressure effects upon the emerging nerve roots or upon the cord itself. These exudates might occasionally undergo spontaneous resorption, but they not infrequently became organized with an inevitable permanent influence upon the nerve tissue. If we are justified in applying these results to human cases, clinical findings are more easily explained. The theory of a primary nervous origin of arthritis deformans no longer finds any measure of general acceptance.

The infectious nature of "rheumatoid arthritis" in adults was probably first given a substantial foundation by Schüller[24] who found a special type of bacillus in the proliferated synovial fringe. This was followed by the reports of similar observations, some discovering diplococci rather than bacilli. The only reported recovery of microörganisms from the affected joints of children was that of Spitzy[20] who resected under strict aseptic conditions small bits of synovial tissue in which he found cocci about the size of the gonococcus. He was able to cultivate these organisms and observed that with certain stains they resembled bacilli. After repeated attempts he was able only once to obtain the organism in another case by joint puncture. Izeke[30] has very recently given his experience in the case of a child, two years of age, suffering with Still's form of chronic arthritis who died of a complicating measles-pneumonia. A hemolytic streptococcus was obtained on blood culture before death, while in the post-mortem examination this same organism was found in pure culture from the spleen, endocardium, and lung. Unfortunately no report was made of the bacteriology of the joints, synovia or bone.

The same organism was found in an undiagnosed mastoid abscess. While there might be a temptation to agree with this author that the arthritis has its origin in the mastoid infection, it must be admitted that the infection was of recent origin secondary to measles.

The experimental production in animals of pathologic changes resembling those of arthritis deformans dates from the work of Poynton[31] who isolated a diplococcus from the joint of an old man suffering from a chronic non-suppurative arthritis and injected the cultured organisms into rabbits intravenously. Two months afterward there was atrophy of the muscles of one thigh and leg, and when the animal was sacrificed about four weeks later there were found changes in bone and cartilage such as are seen in the adult forms of rheumatoid arthritis. There was little damage to capsule or synovial membrane. Of special interest was the long period of latency and the slowness of progression and the slightness of acute disturbances.

The next important work was that of Koch[21] on dogs, later confirmed by Nathan,[19] in which it was shown that the intravenous injection of the hemolytic streptococcus into rabbits may be followed by any degree of joint reaction—from the most severe acute to one insidious, torpid and progressive.

There are three places the organisms are likely to settle; these are subperiosteally and near the joint, subchondrally and still further from the cartilage and, finally, in the bone itself. In each of these foci, depending upon factors not made clear, there was an extension of the infection with tissue reaction of varying degree and kind. Especially germane to the form of the arthritic disease in childhood seems to be the subperiosteal localization, for it is from this spot that the infection spreads to the neighboring joint capsule. It will be seen later that capsular and synovial pathology are early and prominent features of the diseases. In these experiments microörganisms could rarely be found in the synovial membrane unless there was a primary subperiosteal nidus. Where the infection commences in the subepiphyseal region near the provisional line of ossification, changes in the cartilage usually follow which are varied in kind and degree. In one and the same preparation one may find advancing and regressive, proliferative and atrophic processes going on simultaneously. Where the initial process is still deeper, it is possible that the resulting effects are not as likely to become clinically manifest unless it be in the case of Perthês' and Köhler's disease. Axhausen[32] has suggested that these bone lesions are at the foundation of these two forms of osteochondritis. As might be expected, there may be a combination of any of these three types of reaction, especially after the disease process is of several years standing.

If we are to assume for the moment that infection plays any considerable rôle in the causation of the deforming arthritis of children—a theory borne out by the frequent history of preceding infection or infectious disease—it next becomes necessary to determine its origin and mechanism, in other words, the portals of entry of microörganisms. Here we are compelled to rely almost wholly upon clinical observation. Many years ago Trousseau commented upon the association of "angina faucium" and acute rheumatic fever and a causal relationship is quite generally accepted at the present time.

In the case of chronic deforming rheumatism, however, the medical mind while recognizing the general comparability of the two types of disease, was slower in constructing a concrete idea of the nature of the infection. This may be seen in the statement of Whitman[33] who says, "if rheumatoid arthritis is to be considered of infectious nature, its distinction over ordinary forms of infection is certainly marked. . . . One must presuppose a focus of infection within the body which is constantly active."

Billings[34] and his co-workers were among the first to put this view into practical application but this was almost exclusively in adults. Still,[13] while giving due consideration to the possibility that infection might be an etiologic factor, did not pursue the matter further; and, in an extensive perusal of the literature one is struck with the dearth of clinical investigation which might help to throw light on this important problem. It is true that Lindsay[35] in reporting 19 cases of rheumatoid arthritis recommended that there be systematic examination of all the orfices of the body, mouth, nose, ears, rectum, and vagina, and indeed urged that the infected focus if found, be eradicated. He failed to state, however, whether he had done this and, if so, his patients had been benefited.

Of the possible atria of infection in the upper respiratory tract may be mentioned tonsils (faucial and pharyngeal), adenoids, accessory nasal sinuses, teeth and gums, and the structures of the ear. All of these have been implicated in the adult. The removal of the tonsils has not been a very effective measure in the experience of Hammond[36] and this has been recently confirmed.[37] I have, however, personally seen the complete cessation of subacute febrile and joint manifestations follow the removal of the lingual tonsil. That a chronic infection of the nasal sinuses is of not infrequent occurrence in infancy and childhood has only recently been appreciated,[38] so it is not surprising that an attempt should have been made to determine whether or not such an infection is to be regarded as a cause of deforming arthritis.[37] The number of cases reported is small but the results of radical surgical treatment of infected nasal sinuses is suggestive and might well be given further trial. There have been no reports of cases in which the removal of infected teeth would indicate that this type of infection, stressed in adults, has given relief to children. There is likewise nothing more than the indirect evidence in the case reported by Izeke that would inform us as to the importance of the mastoid as a possible focus of infection. We must also consider the possibility of other foci stressed by Nathan that the organisms about the joint may become a focus of infection. Until the cases studied with these points in mind increase in number, it will be impossible to speak with any great degree of authority on the question of the most frequent points at which infecting microörganisms gain entrance to the circulation to be carried to the several points of election in and about the joints.

If we may rely upon the animal experiments and the bacteriologic studies of human cases we must assume that organisms of the hemolytic streptococcus type are the commonest exciting factor. A number of years ago, however, French clinicians of whom may be mentioned Barjon,[39] and especially Poncet,[40] concluded that not only might there be more or less acute joint manifestations in patients suffering from tuberculosis but that a not inconsiderable number of cases of arthritis deformans in adults and in children were due to the tubercle bacillus. A lively dispute has raged over this question and the matter is not yet settled. As most of the evidence and argumentation is clinical in character one is compelled to choose between one personal view as against another, for the clinical picture of Poncet's second peri-arthritic form is practically indistinguishable from the non-tuberculous disease. If it is the tubercle bacillus that produces the lesions, then it must in this form have lost its power to lead to caseation, but if we are to assume a toxin action then the existence of a Poncet's must be admitted. The presence of a positive cutaneous reaction to tuberculin is of itself no evidence that an associated joint lesion is due to the tubercle bacillus, and the fact that joint reaction follows the subcutaneous injection of this substance cannot be taken as indicating a tuberculous lesion, as joint reactions may be elicited by the injection of non-specific proteins and such inert substances as sulphur in oil. There remains the possibility that we are dealing with a double condition, namely, arthritis deformans in a child who has a tuberculous lesion elsewhere. Evidence suggesting this is the beneficial effect of surgical treatment of the nasal sinuses in a case which might have been called Poncet's disease because of a positive tuberculin reaction.[37]

Aside from the academic interest, it is important that an understanding be reached as to the etiology of this syndrome because therapy must depend upon whether we accept the idea of single or dual causation. There is a need for more intensive bacteriologic, clinical and experimental work before a decision can be reached.

While there is to be found in the literature the expressed opinion that the spirochete pallida may be the sole cause of arthritis, [41, 42, 43] the same objections may be raised as in the case of the so-called tuberculous arthritis deformans. The number of cases of assumed syphilitic origin is much smaller as well.

The pathologic changes produced by the gonococcus are usully in the joint itself and although ankylosis may result even in infancy, a statement disputed by Marfan, there is no reason why the disease should be regarded as deforming arthritis. This is certainly true from a clinical standpoint.

The question as to why the microörganisms should select the joints has given rise to the view so stoutly championed by Rosenow[44] and again newly asserted by one of his workers,[45] that bacteria isolated from a case of joint (or other organ) disease have the tendency to localize in the same tissues when inoculated into animals. This has not found general acceptance. The idea of a joint sensitization or increased susceptibility through repeated minimal infections in infancy or early childhood has also been put forward. While some have believed that there was experimental evidence favoring this view, Swift and Boots[46] have not been able to confirm this. It is certainly true that a previous attack of acute articular rhematism is rarely, if ever, followed by arthritis deformans. Lehmann[47] suggest the possibility of a constitutionally weak epiphysis, but fails to offer any very convincing evidence for this.

Hirsch[48] has recently pointed out that in Germany since the war there has been an increase of arthritis deformans, osteoporosis, osteomalacia, and rachitis tarda. At first glance one might be tempted to conclude that the hunger dystrophies prediposed to joint infection. It must not be forgotten that certain dietary errors also lead to a lowering of resistance to respiratory infections. It is obvious that if rickets is actually a predisposing factor in the production of arthritis deformans, then we should expect to see such joint affections of infants and children much more frequently than at present.

With the experience gained in treatment of arthritis deformans in adults by the ablation of assumed foci of infection it was soon learned that cure did not always result and the same observations have been made in juvenile patients. This has led to the thought that some other factors than infection have their part either as cause or predisposing factor, or reason for chronicity and resistance to therapy. Of these may be mentioned the static,[49] mechanical, or traumatic factor. Axhausen[32] and others have found it possible by the use of chemical irritants, and by excision of bits of cartilage to produce in aminals the pathologic picture of arthritis deformans. The question arose as to whether the primary and sterile injury to the joint surface rather than the resulting static disturbance was not the cause of these changes. Wehner[50] excised the patella without injury to the joint, and was able to show that there also developed a pathologic picture of arthritis as seen in the adult or in the later stages of the disease in childhood.

What may we infer from experiments of this sort? In the first place, it is the almost unanimous opinion of the most qualified observers[17, 18, 19, etc.] that it is not possible to draw any positive conclusions as to etiologic factors from the histologic pictures of diseased joints. Clinical experience furthermore teaches us that mechanical disturbances are not the probable causes of the disease in childhood. Then, at this age we have to deal chiefly with capsular changes, such as were not encountered in the experimentally produced joint changes just referred to. It is possible, though, that after a certain degree of joint pathology is once established, mechanical and traumatic factors play a part in making the process the more chronic. We shall have to consider this point once more in discussing the therapy.

Many authors speaking of the disease in adults lay great stress upon gastro-intestinal symptoms, such as constipation and an assumed toxemia to which they give a causal or at least an aggravating rôle. Others have assumed that there are intestinal foci of infection. In a few of the juvenile cases there has been reported a preexisting or intercurrent diarrhea. It is not an easy matter to evaluate the part played in this disease by these manifestations, but we may find a hint in the early observations that intestinal pathology, notably appendicitis, was associated with respiratory (tonsillar) infection, and regard for the time being at least that we are dealing with secondary effects rather than with causes. Koch found not infrequently that there was a severe enteritis following the injection of streptococci in his dogs. As our patients become more and more helpless and bedridden is it any wonder that a high degree of intestinal stasis should result? By the same token a measure of general relief might be expected from assistance given to the sluggish functions. There is not at present much evidence to support the view that the intestine acts as an atrium of infection.

Two very interesting clinical reports [51, 52] call our attention to the fact that there may be joint responses of severe and possibly of chronic character arising from protein sensitization, either from ingested food or even from homologous fluids such as pleural exudate. This brings us to the necessity of further study of the relationship between allergic phenomena and chronic joint disease, for the mention of skin rashes in the various case reports is so frequent that there may be more to this than appears at first glance.

The rôle played by the ductless glands in the chain of events which constitutes the syndrome of deforming arthritis may be dismissed with brief discussion. The rheumatic disease occurring at the menopause is one of the bits of circumstantial evidence which suggests a relationship. The supposed benefit derived from thyroid medication has also led some to conclude that an endocrine factor is at work. It should scarcely be necessary to warn the physician against dogmatic conclusions in any matter of the therapeutic action of the ductless glands and all the more in this disease.

We come finally to the contributing factors mentioned in most of the works of older writers, such as dampness of climate, insanitary dwellings, chilling[53] and exposure. In the case of the disease in childhood, it may be said that these conditions are not invariably encountered, and so the part they play can only be conjectured. It may be that the lack of sunlight and faulty diet so often bound up with unhygienic surroundings, tends to lower the resistance of infection. An hereditary or familial prediposition has also received consideration as one of the contributing accessory etiologic factors.

Were it not for the fact that a history of rheumatism is commonly obtained in the routine of history-taking, one might be more convinced of the significance of this factor. Still controlled this phase of the question in his cases by comparing an equal number of non-rheumatic histories and was unable to find a preponderance of a rheumatic taint in either series. I have, however, seen two typical severe cases of arthritis deformans in brothers.[37] The occurrenc of osteo-arthritis and of arthritis deformans in the members of the same family has also been noted.[47, 55] In the light of our present knowledge then it is safe to assume that infection is the one most important exciting factor. Possible contributing causes may be heredity and familial conditions, previous minimal infections of the joints, nutritional dystrophies, lowering of the bodily resistance to infection, static and traumatic irritation, and possibly protein sensitization. The continuity of the disease process may depend upon the great difficulty of removing the exciting cause and the fact that a distinct amount of joint destruction having occurred, restitution is practically impossible. Permanent injury to the nerve roots or spinal cord, resulting from infection may also interfere with recovery. It may be that secondary "neurotrophic" changes play a much more important part in the general pathology of the disease than is commonly believed.

Classification.—We are confronted with a real difficulty when we attempt to settle upon a satisfactory basis for a classification. We are very positively told, for example, that we must expect no assistance from pathology, that there is little relationship between tissue studies and etiology and clinical form of the disease. The terms "atrophic" and "hypertrophic" no longer find approval. Then, the uncertainty as to the etiology does not make the decision any easier. Even from a clinical viewpoint there are obstacles, the chief one of which is the possibility of confusing degrees of severity with different forms of the disease. Just as there are varying reactions to a typhoid infection so there are differences in the form, severity and course of the disease under discussion. Thus, in one instance we encounter high fever and marked local reaction, while in another the process is more insidious and torpid. Another complicating factor is the matter of those cases reported by Still.[13] Of 22 patients he set aside 12 in whom there were marked enlargement of the spleen and the lymph glands and a tendency toward the development of pericardial adhesion.

To my mind there is not sufficient evidence at this time to warrant the separation of this "form" of the disease from the general group, unless it be to specify those in which his findings are present to a very marked degree, and speak of them as Still's type, and never of Still's disease. The clinical manifestations vary somewhat with the duration of the disease and so what might have earlier seemed to have been the capsular form, later becomes more chondral. Even if we could be sure that there was a parallel between the degree of local reaction and the febrile course and the enlargement of those organs which indicate infection, we would still not be better off. Some writers have spoken of a post-rheumatic form of the disease. Here again there is a possible source of error in that the acute febrile stage of invasion may have been confused with acute articular rheumatism. For the present the wisest course seems to avoid any hard and fast scheme of subdivision of the disease into groups.

There may be some justification for the provisional separation of those cases which are assumed to be due to known causes. It has not been finally settled whether a Poncet's "rheumatisme tuberculeux" is a clinical entity. There is also an increasing tendency to regard syphilis as a cause of arthritis deformans. Later it may be necessary to make a separate place for allergic rheumatism deformans. The gonococcus is also held responsible for some cases of this disease. In the light of our present knowledge it is safe to say that with the possible exception of the first named tuberculous type these latter may constitute only a small percentage of cases encountered.

Clinical Signs and Symptoms.—While there is a wide variation in type, severity, and course to be encountered in this malady, there is a fundamental uniformity which makes a definite symptomatology of the disease.

There may be a previous history of some respiratory infection, contagious disease or exposure to cold. If questioning were to be more close it might be possible to elicit the fact that there had been one or more attacks of rheumatoid pains. Sometimes parents have not been able to notice any departure from the normal.

The age of onset varies, but enough cases have been reported in which the first symptoms occurred early in the second year to justify emphasizing this point. In Saupe's[56] patient signs of the disease were noted at 13 months. A congenital case has been reported.[57]

The sexes are about equally attacked. Sanitary conditions of the home play no deciding rôle in the frequency of the disease, although it appears that more cases come from the homes of the less well-to-do. More cases may be expected from those regions in which there are extremes of climate and dampness. Life in the country is no protection.

In a majority of cases the onset is insidious. The patient will be indisposed, becomes easily tired, may limp, and even try to avoid walking in the event that the foot is first to be involved. So vague may these troubles be that days, weeks or months will pass before the mother comes to realize that something is definitely wrong. The difficulty is not infrequently attributed to a fall or slight injury requiring simple household remedies. Flat-foot has been suspected. Even when professional advice is sought for diagnosis is difficult because of the lack of demonstrable findings. After a while there develops a distinct tenderness on passive or voluntary movement and a doughy swelling is seen on the dorsum of the affected foot. There now may be a stationary period or a subsidence of the trouble. After an interval from one to six months involvement of the knee may be expected, usually on the same side, and, here again, the progression is slow and insidious. I have not been able to find any note or communication to indicate that the initial para-epiphyseal periostitis, observed in animal experiments, gives sufficient symptoms and signs to be complained of by the patient or noted by the mother or attendant. It is not likely that many examinations have been made with that point in mind. In this new involvement there may be at first no more than the vaguest distress. Soon, however, there is seen a visible swelling and an increase in size of the knee as a whole. On examination the swelling will be found to be in the capsule and we know that the cavity is intact, except for possible involvement of the synovial membrane. Pain is usually slight and the unwillingness to walk is more often an indication of the sensitiveness of the patient to the discomfort than of the actual soreness. Passive movement which shows some limitation, is somewhat painful. Pain is rarely great at any stage of the disease although handling may be resented.

Sometimes the knee joint or the spine is the first to be attacked and, as this may be the only localization for a long period of time, may lead to a faulty diagnosis and treatment. The further invasion follows no definite or fixed rule. It may occur in the upper extremity of the same side or the articulations of the other leg. The hip and shoulder joint may be spared for some time. Periarthritis of cervical spine with moderate limitation of motion is sometimes seen early. Temporomaxillary involvement is one of the less common but more distressing features. The phalangeal, carpal, metacarpal, tarsal and metatarsal joints are frequently involved although the toes themselves are occasionally affected. Still states that "extensive deformities of the hands are unknown." This may have been true in the cases which he observed but is certainly not the rule, even though the extreme deflections seen in the hands of older adults are not to be expected.

A remarkable temporary subsidence of the disease may take place sometimes spontaneously. This may lead to the thought that a cure has taken place and by the same token may make it difficult to form a true estimate of the influence of therapeutic attempts; but recurrence is almost sure to occur even after a year or more provided that there has been no success in arresting the disease process. The apparent lessening of the swelling about a joint may also deceive the observer into expecting a dessation of the pathologic process, whereas in reality it means that fibrous contraction and scar formation is taking place. The immobility of the joints is largely due to this. Crackling and grating sounds produced by passive motion are sometimes present but do not, according to Spitzy,[20] signify pathologic changes. With the greater progress of intra-articular disease there results dislocation or bony or fibrous ankylosis, dislocation being common.

Physical examination of the involved joints gives results varying with the degree of reaction and the stage of the disease. In the small joints, for example: There may be no more than a doughy swelling of the peri-articular tissues which causes an elevation of the overlying skin. There is rarely any reddening, and usually only slight tenderness on pressure and passive motion. Later, after muscular atrophy has taken place the articulation stands out in contrast with the bone shaft and appears to be enlarged. As a matter of fact, no great increase in size takes place. In the stage of capsular contracture some deformity and distinct limitation of movement is present. In the case of the knee or elbow joint, for example: Where the periarthritic tissues are more easily made out, the first findings are usually a slight though distinct thickening of the capsule. The patella may float where the joint exudate is considerable. Here again it is the muscular atrophy which makes the joint stand out in relief, as it were, whereas there is not much increase in diameter. Tenderness and limitation of motion vary within wide limits but are almost always of measureable quantity.

Muscle atrophy is seen early, especially about the larger joints and is extreme in advanced cases. Contracture of the muscles is almost invariably present and unless combatted leads to fixation of the limbs in unfavorable positions and is also responsible in part for the obstinate dislocations just mentioned.

Sweating is a common manifestation and is usually independent of fever, is more often slight and continuous, and but rarely drenching in character. It is not uncommon to see beads of sweat on the face and forehead, and upon the hands which are cold and clammy.

Glossy skin—a possible neurotrophic disturbance —is seen over the joints and later over the wasted extremities. A slight exophthalmos occasionally occurs and in one case alopecia[58] is reported.

Fever is present in two forms as pointed out by Still. It may be high and come in two or more day periods, or it may be low, irregular and more or less continuous, rarely reaching 101°F. Sometimes the temperature takes on a septic character. It is rarely entirely absent. Skin reactions of the nature of simple or exudative erythema, often associated with a flare-up of the arthritic process have been described by several observers.[58, 60, 61] This probable allergic reaction is not necessarily excited by foreign protein but may in some way or another be associated with infection.

Cardiac involvement is the exception unless it be that which is encountered in the more acutely febrile cases of the type described by Still. Valvular disease is rarely to be expected, but chronic fibrinous pericarditis is characteristic. Adherent pleura may also occur. There is nothing to show that this has anything to do with the reported existence of a pneumonia prior to the onset of the arthritis.

The gastro-intestinal symptoms are uncharacteristic, with anorexia and constipation the outstanding complaints. Abdominal pain is sometimes present. This may be due at times to referred pains from adherent pleura. Diarrhea[59] is only occasionally encountered.

The psychic reaction varies somewhat with the mental make-up of the patient. One child will be constantly fretful, fearful of the approach of the physician or attendant, while another endures his suffering in a stolid manner. That there should be a degree of nervous exhaustion will surprise no one who has had occasion to become familiar with the disease. In the more acute varieties there may be a considerable toxemia with the suggestion of a severe illness. This is seen usually in fatal cases.

In most instances, after the disease has been present for a number of years, where it has been impossible to arrest its progress, emaciation becomes extreme. The little patient, bedridden and helpless, presents the picture of a living skeleton. Movements and handling are painful, the extremities are fixed, and there is nothing left but the terminal infection. An uncommon instance of survival into adult life is described by Eliakam.[62] A man of 58 years, showed a high degree of retardation of skeletal development and marked deformity, in spite of which handicaps he was able to get about with the aid of crutches.

A moderate secondary anemia is usually present. The leukocytic response varies within rather wide limits, from an occasional slight leukopenia to a leukocytosis varying from 20,000 to 30,000. These figures favor the conception of an allergic bacterial origin of the disease. Except for the lessened secretion of hydrochloric acid,[63, 64] there are no important biochemical changes.

A few illustrative cases are appended:

Case reported by G. Izeke.

C. K. Born June 13, 1920.

F. H. F. H. The mother as child had been a patient at the Children's Dispensary. Father has night-sweats and coughs a great deal.

P. H. Normal delivery. Child very small, but birth weight unknown. Breast fed for six months and then weaned, thriving all the time. Cut first tooth at 11 months and walked shortly afterwards.

P. I. About Christmas of 1921, when the child was 1½ years old, it developed an acute respiratory infection, coughing a great deal and having a high fever. The hands and feet were swollen. In February the temperature again rose and there appeared a marked swelling of the knee and elbow joints. Later the mother noted a stiffness of the neck with limitation of motion. There were periodic attacks of vomiting and diarrhea, lasting two or three days. Edema is said to have been present previous to these attacks but to have disappeared as quickly when the acute gastro-intestinal symptoms had passed. Appetite usually good except at the time of the spells. On admission to the hospital the child appeared extremely sick with anxious facial expression. Emaciation was extreme. The dry skin could be lifted in large folds. In the angle of the jaw, in the axilla and the groin were seen and felt masses of lymph glands as large as hazelnuts. These were firm and easily moveable. In the axilla they were imbedded in a spongy tissue mass. The head and spine were held stiff with backward movement but not rotation painful. Extreme muscular atrophy especially of the extremities. Of the other joints, the elbows, hands, hips, knees, and feet were most affected. There was dislocation of the right hip. The joints involved were all fixed to a more or less degree and were painful when manipulated.

Slight increase in cardiac dulness. Coarse râles in the lungs. Urine was negative. Hb. 56 per cent. W.B.C. 18,000. R.B.C. 5,400,000. Wassermann reaction negative as were all tests for tuberculosis. During the further stay in the hospital, the child had several attacks of fever as high as 104; but in spite of this there seemed to be some improvement and the dislocation of the hip was spontaneously reduced. Death from pneumonia following measles.

At post-mortem the pericardium was found adherent posteriorly. Moderate splenic enlargement. Bones and joints grossly negative. Absolutely no evidence of tuberculosis. Pus in both middle ears. Streptococcus viridans in practically pure culture from endocardium, spleen, lungs and middle ears.

F. M. Age 10. Admitted to the hospital October, 1916.

Both parents nervous. Mother had two miscarriages. One child died at eight months of digestive disturbance.

Breast fed for eight weeks. Teeth at 10 months, walked at 15 months, and talked at two years. Measles at five.

Sick six months before. Knees became painful. Patient tired easily and walked with difficulty. Then had a severe headache and dizziness. Hands, fingers, elbows, knees, feet, and toes became swollen and painful. There was pain in neck and difficulty in turning the head. Pleurisy also present. The child improved for a while, but after climbing out of bed showed re-involvement of the joints. Further course unknown.

Diagnosis.—There is no other disease which is likely to be confused with a fully developed case of arthritis deformans of childhood. The etiology may be unclear but the disease picture can scarcely mislead. In the early stage of the disease there are two facts which may make the diagnosis difficult. These are the involvement of but one joint and sometimes the early age of onset. Where there is a chronic painful affection of one joint, the first thought is naturally of tuberculosis. There should be little difficulty in ruling this out or verifying it by the application of the tuberculin test. It may be necessary to use the more sensitive Mantoux intradermal application of tuberculin. The *x*-ray early reveals changes in the bone in tuberculosis, whereas in arthritis nothing is seen in the roentgenogram other than the evidence of periarticular thickening. There still remains the possibility of Poncet's disease, but as the separate identity of this syndrome has not been established, this offers no real difficulty of diagnosis. Spondylitis of arthritic origin may suggest beginning Pott's disease, but here again the history, roentgenogram and serologic tests will usually give the correct answer.[65]

Gonorrheal arthritic ankylosis can also be excluded in a manner that must be obvious.

Perthes' and Koehler's disease may be diagnosed by the early bone changes and the absence of a reaction for tuberculosis. Gout probably does not occur in early childhood.

Syphilis is an uncommon cause of any syndrome which might be confused with arthritis deformans. The Wassermann test would, of course, be of significance.

The co-existence of arthritis deformans with tuberculosis and syphilis has been mentioned as a possibility to be reckoned with.

In very young children scurvy might be thought of, but the therapeutic test will quickly determine how much foundation there is to such suspicion. As will be seen, the diagnosis in the early stages is not always easy though its importance is obvious.

In view of the recent interest in allergic reactions in joint pathology, protein dermal tests may be carried out. The skin reaction may be controlled by the administration of food which may give a similar reaction. In this way it is possible to determine whether there is a demonstrable harmful effect from a particular food.

In those cases where the fever is high and the progress of the disease is rapid, one might suspect a sepsis or bacteriemia with secondary involvement of the joints. The history will help to clear up the diagnosis, as, for example, in the case of Izeke. However, in such a case it seems to me it is to the patient's advantage to adhere to the original diagnosis and to treat accordingly.

The hemophilic joint[66] is usually more acutely involved and the extravasation of blood in the neighborhood or in more distant parts, makes the diagnosis easy in most cases. Questioning will bring out the history of the disease in other members of the family.

The *x*-ray is of negative rather than of positive value in diagnosis. That is to say, it is the absence of findings rather than their presence which makes for the diagnosis of arthritis deformans of childhood. In the later stages of the disease when cartilage and bone changes have taken place, it is often necessary to rely upon the history and the physical examination, while the roentgenograph merely serves to reveal the amount of destruction that has taken place.

Treatment.—For the physician to stand by idly while a child is slowly but inevitably losing the power of movement is no pleasant experience, and yet this is the case where the attending physician cannot decide how best to intervene to arrest the progress of this disease. It is necessary not only to consider attacking the trouble at its probable source but also to make every effort to minimize those local effects already produced. The general attack must take into account the etiology and as this has not yet been finally settled it becomes necessary to choose that treatment which gives the most hope of offering a measure of relief.

It is safe to say that if we incline to the metabolic or nervous origin, our hands are tied. This fact practically compels for the present, at least, the acceptance of the infectious theory as a working hypothesis and the treatment which is implied thereby. There is, first of all, the removal of the probable foci of infection which in children, happily enough, are not as numerous as they are in adults. It has been pointed out that in early cases in children under two years of age the removal of the faucial tonsils may be sufficient to arrest the further advance of the disease. In older children this is almost certain to be insufficient. Other accessible foci are the accessory nasal sinuses, the lingual tonsil, and, in all probability, the inner ear. It does not seem to me that risk of being radical is to be compared with the reproach of conservatism. Even if surgical intervention fails to bring the desired effect it is rarely harmful, and in view of the hopeless outlook, some risk is certainly justifiable. The coöperation of an experienced otolaryngologist is imperative, but is not always easy to secure because of the newness of the intervention, the youth of the patients, and the frequent absence of acute and apparent manifestations in the nose, throat or ear. This last point makes the diagnosis of infection difficult, but it is surprising how insignificant pathologic change in the nasal sinuses, to say nothing of the absence of pus, may be responsible for a large amount of distant trouble. The faucial tonsils are to be suspected first, and then the accessory sinuses of the nose. The lingual tonsils must also be considered and in the more acute febrile cases the possibility of a mastoid infection may be considered. As the number of cases so treated is small, no hard and fast rules can be made. Each case is a law unto itself and must be decided by the physician in charge. It is not to be thought that the attempted eradication of a suspected focus always leads to cure. This is especially true after nasal sinus operations. Healing may be delayed if the nutrition is not correct. A warm climate promotes the more rapid healing of the operated areas.

The teeth do not seem to play the same important part as atria of infection as is said to be the case in adults. Irritation about the gums should be combated and cavities filled where feasible. If the roentgenogram shows deep-seated infection, extraction should be done. There are so few other points at which infecting microörganisms can enter the circulation that there is no need for further statement, other than if the measures have failed to arrest the evidence of infection, little is to be expected from other radical treatment. In the later stages of the disease there is slight benefit from this type of treatment, although a certain degree of arrest of the infection may be brought about.

Attention is next directed to the local manifestations and here we are again confronted with the difficulty that our treatment must, to a certain degree, depend upon our conception of the process going on in the joints and their membranes. If in every case bacteria are found in the capsule, then such active measures as massage, thermotherapy, and passive motion might theoretically, at least be expected to stir up the infection and assist in its spread. On the other hand, if the affected joint be untreated or, worse still, be placed in a cast, the development of the much dreaded contracture or muscle atrophy might easily be favored. According to Rhonheimer,[16] it is not only advisable but even imperative to resort to the first mentioned form of treatment after waiting for the more active manifestations to disappear. If the local implantation of bacteria is believed to come in showers, then it would be logical to attempt to interrupt the flow from the source and then proceed to control the local situation. Besides careful massage and passive movement the application of heat is the next favored measure. Axhausen[32] prefers the dry heat to moist and baking to the electric light bath. Diathermy may also be tried.

With the inevitable feeling that an unequal battle was being waged against the assumed infectious process by the more conventional methods of treatment, resort was had to vaccins and later to non-specific protein, bacterial and otherwise. Of the latter milk, cartilage and sulphur in oil[67] may be mentioned. The results have been quite alike, a general, local, or combined reaction of varying severity, with fever, chills, and swelling and pain in the joints. Following this the patients often were remarkably relieved. There was a subsidence of joint tenderness, an increase of mobility and a feeling of well-being. These benefits were almost invariably temporary in character, calling for repeated injections. During this period relief was experienced, but if the injections were interrupted the disease was again active.

The temporary relief afforded by this kind of treatment suggests that a "resistance" had been interposed between the origin and the terminus of the infection, rather than a real effect upon either one or the other. While foreign protein therapy has fallen into disfavor, it may nevertheless have its place in helping to tide a patient over the period in which the eradication of the nidus of infection is attempted. It may also be used to ameliorate those advanced cases where there is no other effective treatment.

Surgery of the joints has been resorted to in certain adult cases but not to my knowledge in childhood. This has consisted in the removal of the diseased synovial membrane, and is mentioned merely for completeness' sake.

The benefits of climate have been briefly alluded to as being part of the adjuvant treatment. By the same token, the effects of heliotherapy, artificial and natural, should be studied, but at the present time should not be relied upon as the sole treatment.

If this disease is due to infection, then it might perhaps be looked upon as a form of bacterial parasitism due, in part at least, to faulty nutrition. There is some experimental evidence for this. During the clinical study of nasal sinus disease the impression was obtained that it was more often seen in children with rickets. With this in mind it was found possible to produce this parasitism in rats by omission of the nutritive factors of cod-liver oil from the diet. Such infections once established were not easily cured after a certain stage. Even though this latter point apparently holds true in the human, it is important to follow up surgical measures in the nose and throat with a correction of the faulty diet. Milk not too rich in fat, cod-liver oil, and green vegetables are our mainstays in the attempt to bolster up the lowered state of resistance. The anorexia so often present leads sometimes to considerable lessening in the food intake, which in itself may play a part in lessening the defensive powers of the tissues.

Drugs are of no demonstrable value. Salicylates are not indicated unless there is much pain. They are often said to be ineffective. Iodin has long been recommended and while it is possible that it is of service, it is difficult to prove this. Certainly one will not wish to use the immense doses recently recommended by Thiroloix.[68] This author has thought that he has seen benefit from the daily intravenous injection of from 5 to 10 c.c. of a 10 per cent. solution of a special combination of iodin, benzylalcohol, and hexamethylamin. The good results claimed for thyroid medication were seen chiefly in adults. Arsenical compounds are also mentioned as worthy of trial. They will do no harm if used in moderation and might conceivably improve the general nutritive state.

The digestive tract calls for careful attention. A lowering of the secretion of hydrochloric acid is sometimes present. The administration of this acid may be of value also because it combats the constipation and intestinal putrefaction found in so many cases. The other common methods of treatment of these conditions are also indicated, especially in bedridden cases.

The disease once having reached a certain stage of advancement, there is little that can be done. It seems almost impossible to remove the cause and the damage already done to the joints is irreparable. The emaciation resists all efforts at correction. The patient is bedridden and helpless, waiting only for the end. Attempts to correct the scar-like capsular contractures have not been very successful. Thiosinamin, formerly regarded as a specific "solvent" of fibrous tissue, has not been of any avail. Rhonheimer states that he has seen good results from the local injection of cholin hydrochlorid, introduced by Fraenkel, injected locally in the amount of 5 to 30 c.c. of a 5 per cent. solution. This is followed within an hour by a hot-air bath. Deformity is to be further treated by orthopedic measures. Ambulatory devices may be of service in the early and intermediate stages of the disease, so that contraction may be avoided and the patient prevented from becoming bedridden. I recall one case in which this was done with the result that the little girl was able to walk after having been in bed for nearly a year.

The discussion of other orthopedic measures does not properly belong in this place. I should like, however, to warn against too long a period of immobilization by plaster-of-paris casts, as it interferes with the application of local remedies to the joint.

As indicated above, the treatment of the so-called Poncet's syndrome is determined by the physician's conception of a single or dual etiology. In the first instance, local treatment of the upper respiratory tract is omitted unless it is decided to remove the tonsils on the assumption that they harbor the tubercle bacillus. Expectant, roborative, and moderate local treatment of the joints is indicated. If the dual nature of the disease is admitted, with focal infection as the exciting cause, then one should resort to those measures just described.

Where syphilis is present the usually employed remedies are indicated.

The importance of early treatment cannot be over-emphasized.

Prognosis.—The viewpoint of some of the earlier writers was rather different from that of the present. In the opinion of Lacaze-Dori, for example: The affection was not infrequently self-limited. Nowadays few would subscribe to this optimistic prognosis. On the contrary, there is a unanimity of opinion as to the almost irresistible progression of the joint involvement with resulting deformity and death after a varying period of from 3 to 10 or 12 years from intercurrent terminal infection. In the more acute (Still's) type death may occur in a short time, but such an outcome is the exception since cases of that degree of severity are not frequently seen. The age of onset seems to have little to do with the prognosis unless it be true in younger patients there is greater chance for the contagious diseases to increase the infection already existing or to lower that resistance to a still greater degree. This possible disadvantage is counterbalanced by the fact that treatment can be commenced before the disease has progressed too far.

It would seem that early vigorous treatment is the most potent factor in affecting the course of the disease. A great responsibility rests, therefore, upon the attending physician who has the power of deciding whether to adopt a policy of expectancy or one of vigorous intervention even in the face of the admitted uncertainty of etiology and consequent lack of a proven therapy.

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